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Original Communications

THE INFLUENCE OF AUTONOMIC IMBALANCE ON THE HUMAN ELECTROCARDIOGRAM

I. UNSTABLE T WAVES IN PRECORDIAL LEADS FROM EMOTIONALLY UNSTABLE PERSONS WITHOUT ORGANIC HEART DISEASE

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INTRODUCTION

THE recent recommendations by the American Heart Association that multiple precordial leads be employed routinely was intended primarily to provide a more exact means of recognizing organic myocardial change.[1] However, my analysis of the electrocardiographic data in a group of soldiers suffering from neurocirculatory asthenia has indicated that, even when the subject is recumbent, and in the absence of genuine heart disease, bizarre T waves which are indistinguishable from those produced by structural changes can occur in chest leads derived from one or more of the several accepted positions to the left of the sternum. A similar observation has been made by Dupuy,[2] but he does not offer any satisfactory explanation for the phenomenon. The purpose of the present preliminary report is, therefore, to display the characteristic responses of these aberrant T waves of "functional" origin to various procedures, and therefrom not only to elucidate the mechanism underlying their causation, but also to provide a simple means of differentiating them from similar alterations of an organic nature.

MATERIAL

The persons who showed these "functional" precordial T-wave changes were male adults who had been referred for a cardiovascular survey because they manifested either signs or symptoms suggestive of structural cardiovascular disease, but who, on subsequent study, were

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found to have functional derangement of the cardiovascular system. They ranged in age from 18 to 35 years; the average age was 27 years. No one body type was encountered consistently; the asthenic, hypersthenic, and intermediate types occurred with about equal frequency.

The symptoms, not all of which were uniformly present in every case, included, aside from nervousness and weakness, (a) dyspnea of the nonhyperventilation type, ranging from a feeling of suffocation to a sensation of not being able to get enough air into the lungs with ordinary respiration; (b) palpitation, usually coming on suddenly and disappearing gradually, but occasionally beginning and ending abruptly; (c) precordial pain, never substernal, not related to exertion, dull and aching in character, limited chiefly to the region of the left nipple, and occasionally associated with "soreness to the touch"; (d) dizziness, not characteristically of the orthostatic type; and (e) pains in various joints unassociated with redness, swelling, or limitation of motion of those structures.

The physical signs, not all of which were uniformly present in every case, consisted of the following: (a) hyperesthesia in the region of the left nipple; (b) a labile blood pressure, with the systolic more variable than the diastolic level; (c) a labile pulse rate which tended to be rapid during waking hours and normal during sleep; (d) systolic murmurs at the base of the heart and sometimes at the cardiac apex, more pronounced when the heart rate was rapid; (e) a poor Schneider index; (f) sighing respiration; (g) cold, sweaty hands; (h) tremors of the outstretched hands; (i) axillary hyperhidrosis during the examination; and (j) ready flushing of the neck and face on slight provocation.

METHOD

Each patient was kept in the hospital long enough to enable the examiners to exclude the possibility of organic heart disease. A careful history was obtained during the first interview, and especial emphasis was placed on factors which might have produced emotional disturbances or an anxiety state. A general assay of the emotional pattern prior to entry into the service was also attempted. In special instances, the assistance of the attending neuropsychiatrist was obtained. A thorough physical examination was conducted immediately after the initial interview, and precautions were taken not to make it appear that the cardiovascular apparatus was being made the object of minute inquiry. In frequent subsequent examinations, the blood pressure and pulse rate in the recumbent and upright positions were carefully checked, systolic murmurs were observed to rule out the possibility of organic valvular disease, hyperesthesia over the precordium was sought for, and the presence of sighing respiration, cold, sweaty hands, tremors, axillary hyperhidrosis, and ready flushing was noted.

In order to obtain corroborative evidence that the heart was not diseased, the following laboratory studies were performed in each case: (a) complete blood cell count, (b) urinalysis, (c) frequent erythrocyte sedimentation rate determinations, (d) a basal metabolic rate estimation, (e) a measurement of blood velocity, and (f) an estimation of cardiac size in the teleoroentgenogram by the method of Ungerleider and Gubner.

In each case, soon after the patient's admission, an electrocardiogram was obtained while he was recumbent and after he had been relaxed

for fifteen minutes and had abstained from smoking for at least thirty minutes. Multiple precordial leads from the left hemithorax were included; an exploring electrode in the C_2, C_3, and C_4 position was paired with the left leg and right arm according to the technique recommended by the American Heart Association.[3] This procedure was repeated at least once every week of the patient's hospital stay. The appearance of an abnormal T wave in any precordial lead was succeeded by the application of the following testing methods, by means of which, in comparable leads, the characteristic responses of the bizarre deflection were graphically recorded:

1. Comparative records were obtained while the patient was recumbent and after the assumption for from three to five minutes of the upright position. Since preliminary studies had indicated that no significant differences are to be noted between the effects induced by a tilt table and those resulting from a postural change accomplished by the subject himself, the latter method was used because of its simplicity. The numbered positions upon the thorax were carefully marked in order to exclude the possibility of malposition of the exploring electrode as a factor in any T-wave alteration resulting from the postural change.

2. The patient then resumed the supine position, and, after he had rested for fifteen minutes, another control tracing was obtained. This was followed immediately by the intravenous administration of 0.5 mg. of ergotamine tartrate, and thirty minutes later, without any change in the position of the patient, a comparable record was recorded.* This interval was selected because preliminary observations[4] had indicated that, in man, the maximum pharmacologic effect of this preparation, which is essentially sympatholytic in character,[5-7] occurs thirty minutes after its exhibition by this route and is sustained usually for sixty minutes longer. In special instances, this procedure was extended to include a record of the effects of postural change while the heart was still under the influence of ergotamine. Also, occasionally, in order to demonstrate the mutually antagonistic influences upon the precordial lead T wave of the sympathetic and parasympathetic components of the autonomic nervous system, tracings were obtained with the subject recumbent while the heart was under the maximal influence of both ergotamine and atropine.† For the latter type of experiment, the effects of ergotamine were registered in the usual manner thirty minutes after its exhibition, immediately after which 2.5 mg. of atropine sulfate were administered subcutaneously, following which successive records were obtained at intervals from fifteen to sixty minutes thereafter.

3. On a different day, a control tracing with the patient recumbent was recorded; the usual precautions regarding relaxation and abstention from tobacco were adhered to. Immediately afterward, 2.5 mg. of atropine sulfate were administered subcutaneously, and then sequential records during recumbency were obtained in successive fifteen-minute intervals for one hour.

4. On another occasion, the sympathomimetic effects of amyl nitrite were registered. The usual control tracing during recumbency was fol-

*The effect of ergotamine tartrate in this dosage on the normal electrocardiogram of a person with a stable autonomic nervous system consists in a slowing of the sinus rate and a slight increase in the amplitude of the T wave in all leads, without any alteration in the form or direction of this deflection.

†The parasympathomimetic effects of atropine may be evident up to fifteen minutes after the subcutaneous injection of 2.5 mg. of this drug, whereas its parasympatholytic properties become manifest from twenty to sixty minutes after its administration in this dosage.

lowed by the inhalation of 5 minims of this drug, and then a comparable record was obtained with the patient in the same position, after a significant fall in the blood pressure and secondary tachycardia had developed.

RESULTS

Distortions in the precordial lead T waves during recumbency occurred in 80 per cent of the cases which formed the basis of this study. In one-fourth of this number, significant corresponding aberrations of the same deflection were apparent in the limb leads in the same record. The characteristics of these bizarre precordial lead T waves are listed in Table I. It will, in addition, be noted from Table II that it is possible not only to classify them as expressions of autonomic imbalance, but also to identify them more specifically as manifestations of hypervagotonia or hypersympathicotonia because of their responses to the testing methods described in the text.

The inconstancy and variability of the precordial lead T-wave aberration in comparable leads in successive electrocardiograms from the same patient were striking features. In each case, it was definitely ascertained that these variations could not be attributed to malposition of the exploring electrode. Occasionally this instability of the T wave was even apparent in successive cardiac cycles in the same electrocardiogram. Most often, the abnormality of the precordial lead T wave was evident in one or more of the CF leads and absent in corresponding CR leads.

TABLE I

"FUNCTIONAL" PRECORDIAL LEAD T-WAVE ABERRATIONS

TYPE OF ABERRATION	VAGOTONIC	SYMPATHICOTONIC
Variations in successive cardiac cycles	++	++
Polarity reversal	++	+
Inconstancy of T-wave alteration in successive routine electrocardiograms	+	++
Notching	–	++
Reduced amplitude	+	++
Upright with blunting of apex	–	++
Associated heart rate	Usually below 75	Always above 75

++ = Frequently encountered.
\+ = Occasionally encountered.
– = Never encountered.

TABLE II

EFFECTS OF TESTING METHODS ON DISTORTION OF T WAVE

	VAGOTONIC	SYMPATHICOTONIC
Upright position (sympathomimetic effect)	–	+
Ergotamine (sympatholytic effect)	+	–
30 to 60 minutes after atropine (parasympatholytic effect)	–	+
Amyl nitrite (sympathomimetic effect)	–	+
15 minutes after atropine (parasympathomimetic effect)	+ or 0	–

\+ = Exaggeration of T-wave distortion.
– = Elimination or lessening of T-wave distortion.
0 = No effect upon T-wave distortion.

The spontaneous appearance of vagotonic precordial lead T-wave aberrations was limited to the CF leads in every case, whereas those due to hypersympathicotonia were sometimes seen in both the CF and CR leads. In no instance were any of these unstable T waves limited to the CR leads alone.

In the group with distortion of precordial lead T waves caused by hypervagotonia, a sympatholytic drug, such as ergotamine, made the deformity not only more pronounced, but also more resistant to the usual normalization which resulted from assumption of the upright position. When such deformed, vagotonic T waves spontaneously appeared in one CF lead and not in another, the precordial T wave in the normal CF lead developed some aberration after the administration of this sympatholytic preparation. It was also observed occasionally that distortion of a precordial lead T wave caused by vagotonia spontaneously disappeared in a subsequent record. In such circumstances the original deformity could be reproduced by the administration of ergotamine. A comparable effect was produced by a parasympatholytic drug, such as atropine, when bizarre precordial lead T waves caused by hypersympathicotonia had similarly spontaneously disappeared, with the exception that in the latter group such induced changes were apparent even in leads employing another extremity for the application of the indifferent electrode.

These bizarre precordial lead T waves caused by preponderance of either cholinergic or adrenergic stimuli did not seem to be brought about by changes in the heart rate, although, in some instances, a direct relationship could not be excluded entirely.

ILLUSTRATIVE CASES

CASE 1.—This 22-year-old Negro was admitted to the hospital because of bilateral parotid swelling. The diagnosis of epidemic parotitis was confirmed by the contagion officer. The clinical course of the patient was uneventful, but, during his convalescence, he complained of a fairly constant ache in the region of the left nipple. Careful questioning revealed the fact that this symptom had been present frequently during the preceding three years, had occurred independent of exertion, and was definitely related to disturbed emotional states. However, because of the presence of a systolic apical murmur, he was referred for a cardiovascular survey after he had made a complete and uncomplicated recovery from his attack of mumps.

Examination on the cardiac service elicited the following: The patient was an asthenic, apprehensive person who had a labile pulse rate which tended to be about 60 during rest, axillary hyperhidrosis, and cold, sweaty hands. There was a short, low-pitched systolic apical murmur while he was recumbent, but it disappeared when he sat up, and it did not, even in part, replace the first heart sound. It was therefore considered to be "functional." All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Repeated electrocardiograms while he was recumbent consistently revealed inversion of the T wave in Lead CF_2, without any accompany-

ing T-wave changes in the limb leads or in the other chest leads (Figs. 1, 2, and 3). On different occasions, the amplitude of this negative precordial lead T wave varied in depth (Figs. 1, 2, and 3). The response of this bizarre precordial lead T wave to the various testing procedures was as follows: The upright position converted it to a positive deflection. This occurred either when the patient was tilted to a perpendicular position (Figs. 2 and 3), or when he assumed the vertical position himself (Fig. 1). Atropinization, after thirty minutes, independent of any postural change, produced a similar effect, but not to a comparable degree (Fig. 1). Amyl nitrite during recumbency produced an effect similar to that brought about by the upright position (Figs. 1 and 3). Ergotamine, with the patient in the recumbent position, had no significant effect on the inverted T wave in Lead CF_2, but it did convert the positive T wave in Lead CF_4 to a negative deflection (Fig. 1).

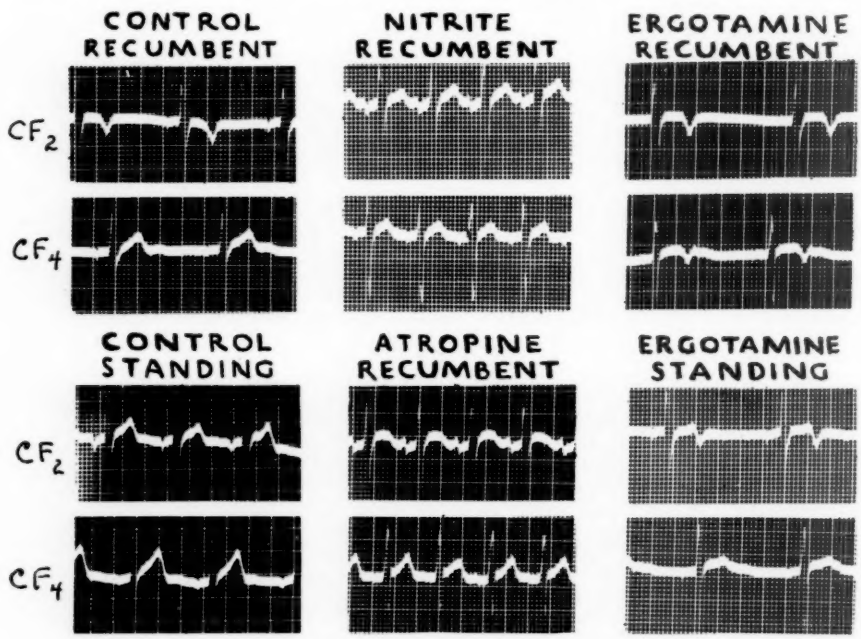

Fig. 1.—Case 1.

Also, while the heart was still under the influence of ergotamine, the assumption of the upright position did not cause the usual reversion of the T wave in Lead CF_2 to a positive deflection (Fig. 1). In addition, with the heart under these combined influences, the T wave in Lead CF_4, although positive in direction, was definitely depressed as compared with the amplitude it attained in control electrocardiograms obtained in the upright position (Fig. 1).

Comment.—The characteristic response in this instance of the bizarre T wave in Lead CF_2 to sympathomimetic and parasympatholytic influences establishes the fact that it was merely a manifestation of hypervagotonia. The ability of a sympatholytic drug, such as ergotamine, not only to prevent the usual effect of the upright position on the in-

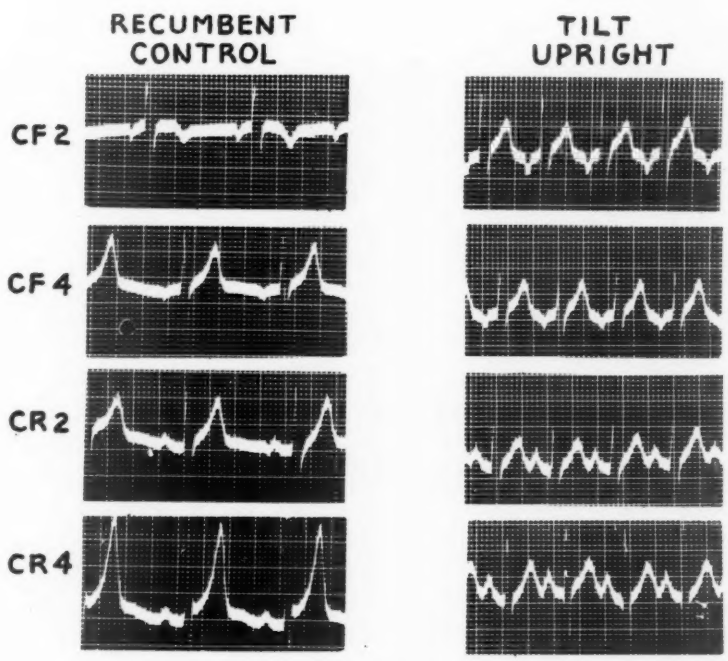

Fig. 2.—Case 1.

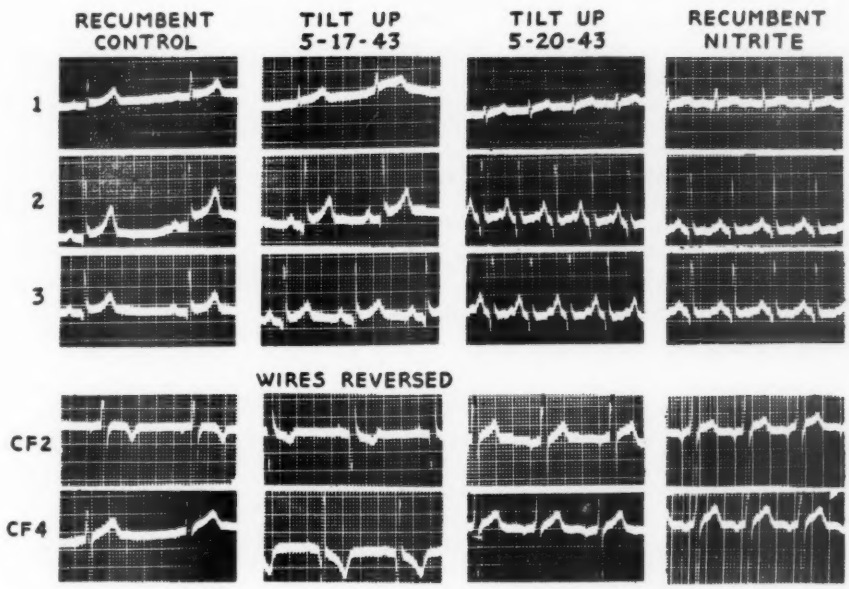

Fig. 3.—Case 1.

verted T wave in Lead CF_2, but also to produce T-wave distortion in Lead CF_4 in the recumbent position is further evidence in support of this view. The latter experiment, in addition, shows conclusively that any T-wave alteration produced by assuming the upright position is to be attributed to increased sympathetic tone, reflexly induced, and not to a change in the position of the heart. Also in favor of this hypothesis are the observations that, in the same case, amyl nitrite, during recumbency, produced T-wave changes in both the limb and precordial leads which were indistinguishable from those resulting from a change in direction of the long axis of the body (Figs. 1 and 3), and that the upright position did not produce polarity changes in the T waves of the limb leads when tachycardia did not occur (Fig. 3). On the contrary, the reversal of the vagotonic inverted T wave in Lead CF_2 to positive polarity as a result of postural change bore no relation to the heart rate (Fig. 3), indicating the fundamental instability of such functionally bizarre precordial lead T waves.

Also, the influence of heart rate in the production of the bizarreness of the precordial lead T wave in this instance appears to be unimportant. The inversion of the T wave in Lead CF_4 caused by a sympatholytic drug (Fig. 1) was associated with a heart rate no slower than that concurrent with a normal T wave in the same lead in a control tracing on a different occasion (Fig. 3), and the positive T wave in Lead CF_2 resulting from assumption of the upright position (Fig. 3) was not associated with a heart rate any more rapid than that which accompanied an inverted T wave in the same lead in a control record obtained at another time in the recumbent position (Fig. 2).

Case 2.—This 18-year-old white man was referred to the cardiac service because a systolic murmur was discovered during his stay in the hospital for an acute upper respiratory infection. No history of antecedent rheumatism or recent polyarthritis could be elicited. Examination revealed the following: The patient was a tall, well-nourished man who was apprehensive, flushed easily, and had cold, sweaty hands, a labile pulse rate, a labile blood pressure, tremors of the outstretched palms, and axillary hyperhidrosis. He admitted being emotionally disturbed, and stated that at one time it was thought that he was developing a "code neurosis." A short, low-pitched systolic apical murmur was heard during recumbency, but it disappeared when the patient assumed the upright position, and it did not even in part replace the first heart sound. It was therefore considered to be "functional." All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Electrocardiograms during recumbency on various occasions revealed an inconstant inversion of the T wave in Lead CF_2, independent of any accompanying T-wave changes in the limb leads or other precordial leads (Figs. 4, 5 and 6), and by careful checking it was made certain that these T-wave alterations could not be ascribed to malposition of the exploring electrode.

The response of this bizarre precordial lead T wave to the various testing procedures was as follows: The upright position converted it to

a positive deflection (Fig. 4). Amyl nitrite during recumbency had a similar effect (Fig. 4). On an occasion, when the T wave was diphasic, ergotamine exaggerated the bizarreness of this deflection, transforming it into a deeply inverted T wave (Fig. 5). Although the upright position did result in a reversal to positive polarity of this ergotamine-induced precordial lead T-wave deformity, this reversal did not occur

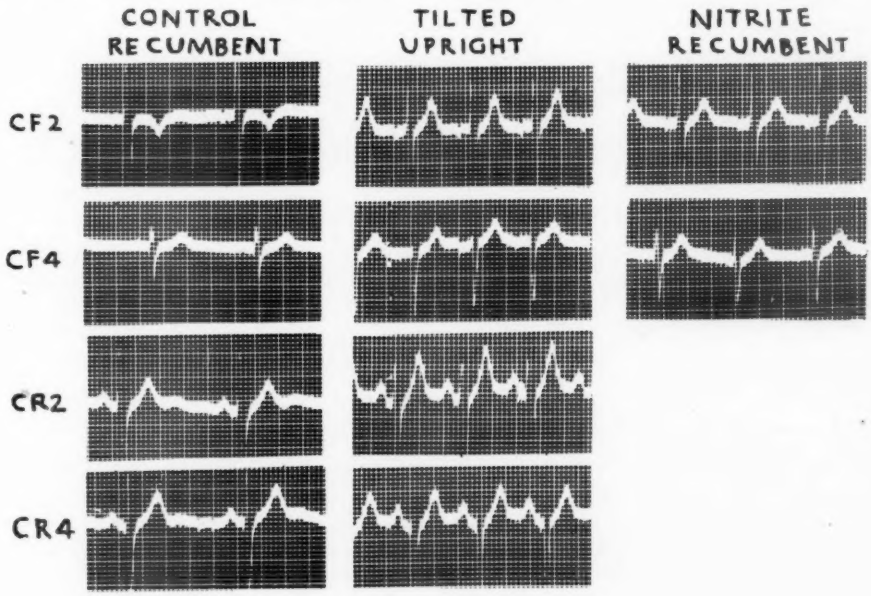

Fig. 4.—Case 2.

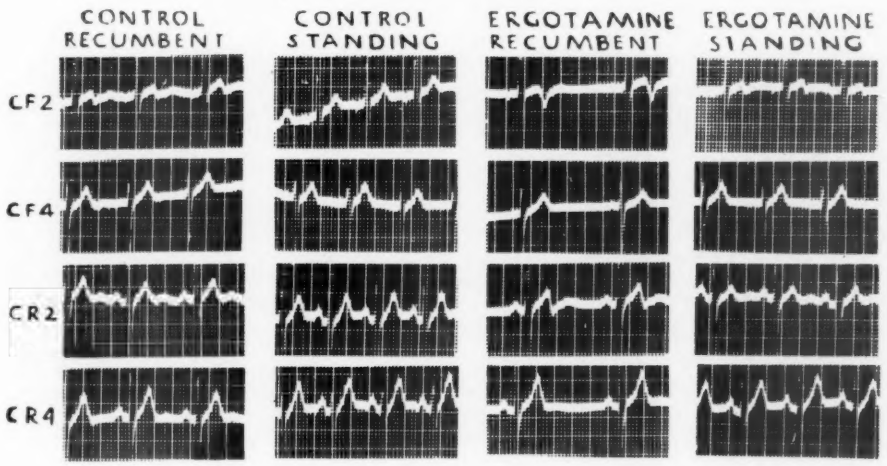

Fig. 5.—Case 2.

to the same extent as that which had been brought about by the postural change immediately prior to the exhibition of this drug (Fig. 5). On another occasion, when the T wave in CF_2 in the control record had spontaneously become normally upright, ergotamine produced a similar

change (Fig. 6); this, in turn, was abolished by the parasympatholytic action of atropine, even while the heart was still under the influence of the former drug (Fig. 6).

Comment.—The characteristic responses of the bizarre T wave in lead CF_2 to sympathomimetic influences (Fig. 4) undoubtedly indicate that this electrocardiographic alteration merely represented vagal preponderance. The nonpersistence of the abnormal T wave in repeated records (Figs. 4, 5, and 6) undoubtedly means that, even in those unstable persons whose vagotonic electrocardiographic pattern is a characteristic feature, the level of "cholinergia" is not constant. For this reason, the instability of the precordial lead T wave obviously is to be related to variations in nerve tone. This concept is an important one, for it can be usefully applied to the proper appraisal of spontaneous fluctuations in form, amplitude, and polarity of the precordial lead T wave in successive electrocardiograms on anyone who presents the stigmas of a functional, rather than an organic, derangement of the cardiovascular system.

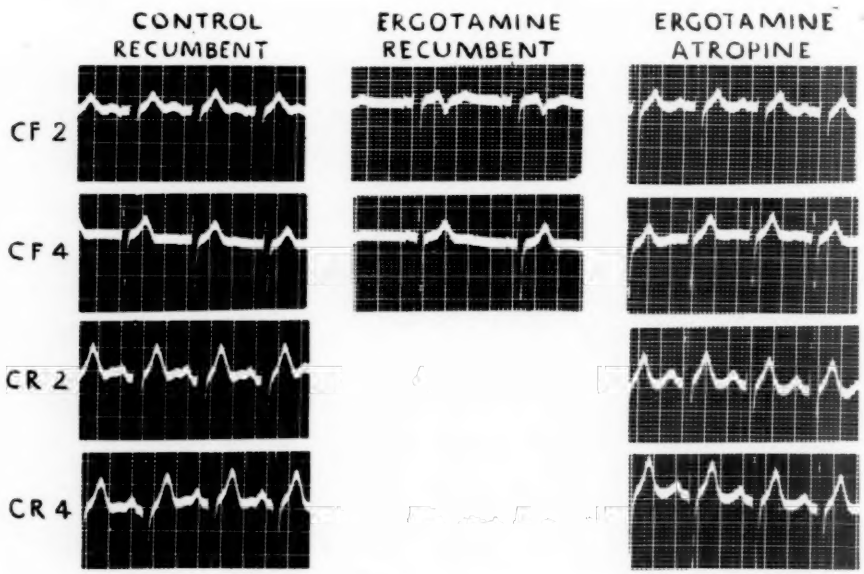

Fig. 6.—Case 2.

Another interesting observation in the study of this case was the fact that, even under circumstances in which hypervagotonia existed in a "latent" stage, such inherent instability of the autonomic nervous system could be made apparent in the electrocardiogram after the supplemental administration of a sympatholytic preparation such as ergotamine (Fig. 6). This phenomenon is especially significant because this drug acts upon the T wave in a directly opposite manner in stable individuals.[4]

Although variations in the degree of aberration in the precordial lead T wave were evident in repeated curves (Figs. 4, 5, and 6), instability of this deflection was seen even in successive cardiac cycles in the same electrocardiogram (Fig. 5). This was not uncommon in the entire group.

It will be noticed that comparable effects were produced by amyl nitrite during recumbency and by the upright position (Fig. 4). This again indicates that the postural change produces its effects, not by a change in the position of the heart, but by a reflex increase in sympathetic tone. This phenomenon likewise serves to show how easily the precordial lead T wave of an unstable person can be influenced by a slight preponderance of one or the other components of the autonomic nervous system, in contrast with the stability of this deflection in the precordial leads from normal adults when the upright position is assumed.[4]

As in the preceding case, the effects of vagal preponderance on the precordial lead T wave were displayed only in a CF lead (Figs. 4, 5, and 6).

The relation of heart rate to the appearance of a bizarre precordial lead T wave appeared to be, in this instance, a close one, for the deflection was most abnormal when the rate was 60 or below, regardless of whether this associated bradycardia occurred spontaneously in a control record (Fig. 4) or whether it was a part of an ergotamine effect (Figs. 5 and 6).

CASE 3.—This 28-year-old white man was referred to the cardiac service because hypertension had been found during a routine examination prior to being commissioned. His complaints consisted of shortness of breath, palpitation, precordial pain, excessive sweating, dizziness, and nervousness. He stated that he had always been "high strung," and admitted that at one time the diagnosis of "code neurosis" had been considered. Examination revealed the following: The patient was a well-nourished man with an intermediate type of habitus, who flushed easily, was apprehensive, and had a labile pulse rate and a labile blood pressure, tremors of the outstretched hands, and axillary hyperhidrosis. Nothing significant was revealed by examination of the heart. All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Repeated electrocardiograms exhibited variations in the precordial lead T waves, characterized chiefly by a reduction in the amplitude and by notching of the apex (Fig. 7). Occasionally, actual inversion of the T wave occurred, especially in the upright position. These changes, but not to the same degree, appeared in all the chest leads and frequently were associated with alterations of the same order in the limb leads. The response of these bizarre precordial lead T waves to ergotamine was normalization of their configuration (Fig. 7).

Comment.—The characteristic response, in this instance, of the bizarre precordial lead T waves to sympathomimetic influences and to a sympatholytic drug establishes them definitely as expressions of adrenergic preponderance. The resemblance of these "functional" distortions of

the T wave to those produced by structural disease is striking. In this case, the occurrence of changes in the CR and limb leads similar to those which were present in the CF leads was not unexpected, because such associated changes seem to be the rule in the "sympathicotonic" group, as contrasted with the absence of such combined alterations in the "vagotonic" group. In this case, too, there were spontaneous fluctuations in the degree of aberration of these T waves in repeated curves, and, because of the symptoms and physical signs, the electrocardiographic changes were originally construed to be evidences of active carditis. However, the application of the testing methods described in the text eventually permitted a proper appraisal, and the conclusion that they were an indication of a functional cardiac derangement was subsequently confirmed by the clinical course.

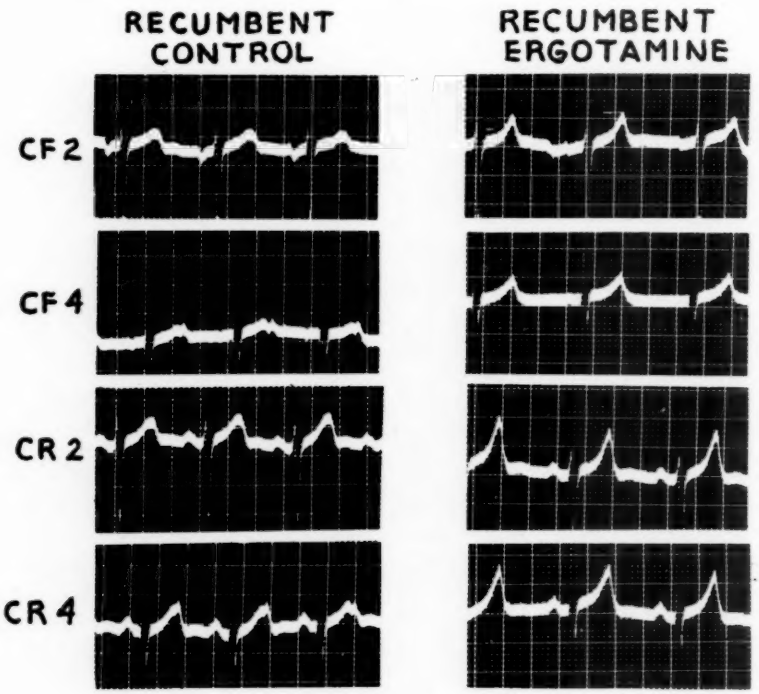

Fig. 7.—Case 3.

The relation of heart rate to the appearance of a bizarre precordial lead T wave in this instance did not appear to be close because spontaneous aberrations in this deflection in the recumbent position were frequently of a higher degree when the rate was below 85 than when it exceeded this level.

Case 4.—A 21-year-old white man was referred to the cardiac service because of an attack of rapid heart action of several hours' duration. The patient stated that he had suffered similar attacks of tachycardia,

characterized by an abrupt onset and abrupt termination, frequently since his adolescence. The precipitating cause was not always evident, but emotional crises seemed to be an important etiological factor. He admitted that he was always a "nervous" person, and that he was easily disturbed emotionally by even relatively insignificant events. Examination revealed the following: The patient was a moderately well-nourished person with an intermediate type of habitus, who flushed easily,

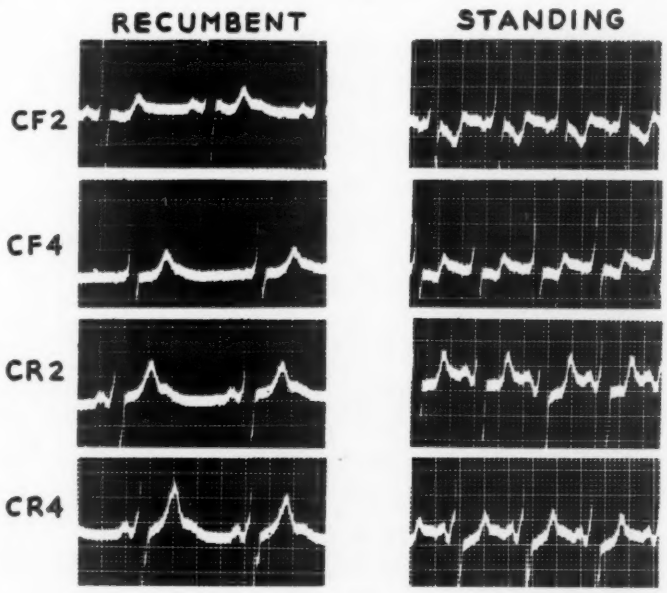

Fig. 8.—Case 4.

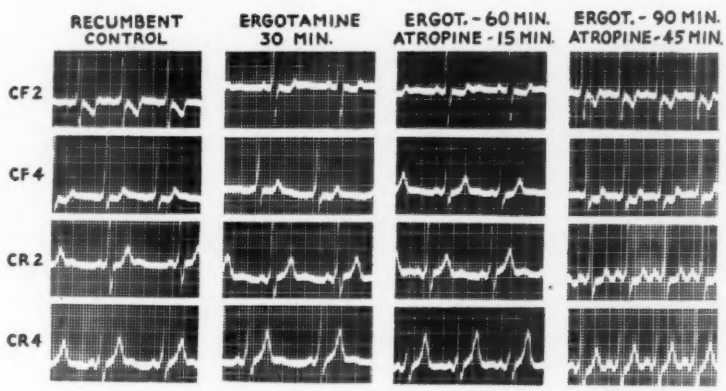

Fig. 9.—Case 4.

was apprehensive, and had a labile pulse rate and a labile blood pressure, tremors of the outstretched hands, axillary hyperhidrosis, and cold, sweaty palms, and who manifested sighing respiration at frequent intervals. Nothing significant was revealed by examination of the heart. All laboratory studies and other diagnostic procedures failed to reveal any evidence of acute or chronic heart disease.

Electrocardiograms, obtained at frequent intervals, revealed inconstant inversion of the T wave in Lead CF_2 (Figs. 8, 9, and 10). In addition, there were constant shortening of the P-R interval and slurring of the upstroke of the R wave; this was diagnostic of the Wolff-Parkinson-White syndrome (Fig. 8). No comparable changes in the T wave occurred in the limb leads at any time. Occasionally, depression of the S-T segment, with a tendency to a diphasic configuration of the T wave, was apparent in Lead CF_4 (Figs. 9 and 10). The response of the precordial lead T wave to postural change, which was recorded at a time when the T wave in the control record had spontaneously reverted to normal, took the form of a marked change in polarity of this deflection in Leads CF_2 and CF_4 and a depression of the S-T segments in Leads CR_2 and CR_4 (Fig. 8). On other occasions, a spontaneously appearing deformity of the T wave in Lead CF_2 disappeared thirty minutes after the administration of ergotamine (Fig. 9) and fifteen minutes after the administration of atropine (Fig. 10). The normalization of the T wave in Lead CF_2 by ergotamine did not persist forty-five minutes after the exhibition of atropine, even though during this time the heart was still under the influence of the former drug.

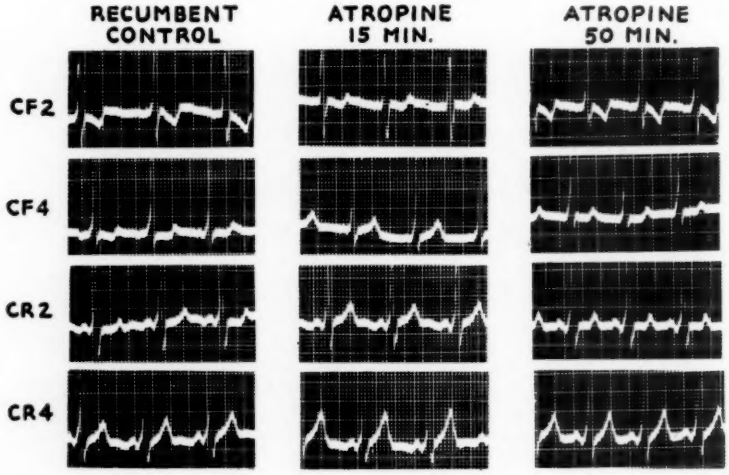

Fig. 10.—Case 4.

Comment.—The spontaneous fluctuations in the polarity of the precordial lead T waves and configuration of the S-T segments were a striking feature in this case, and, in this respect, were characteristic of the behavior of the functionally unstable deflections described in this report. The typical response to postural change (Fig. 8), to a sympatholytic drug (Fig. 9), and to the parasympathomimetic effect of atropine (Fig. 10) establishes the fact that the instability is caused by a state of adrenergic preponderance. The mutually antagonistic influences of the vagal and sympathetic components of the autonomic nervous system on the S-T-T portion of the precordial electrocardiogram are well illustrated in the experiment in which the parasympatholytic effects of atropine became evident while the heart was still under the influence

of a sympatholytic drug such as ergotamine (Fig. 9). Although the presence of the Wolff-Parkinson-White electrocardiographic pattern in this case supplies an explanation for the attacks of tachycardia, there was no apparent relationship between this anomaly and the presence of the unstable precordial lead T waves.

The relation of heart rate to the appearance of the sympathicotonically distorted precordial lead T waves is presumably not a close one, for, at times, a normalization of this deflection was accompanied by a rate more rapid than that associated with a distortion of the same wave (Fig. 10).

DISCUSSION

In previous reports, other investigators have already described electrocardiographic aberrations in cases of neurocirculatory asthenia.[8, 9] These have consisted of S-T segment depressions and T-wave inversions in the limb leads, when the electrocardiogram is made with the subject in the semi-erect[8] or upright position.[9] However, these alterations are of questionable significance, for it has been demonstrated that identical changes may occur in normal, emotionally stable persons,[4, 10] presumably because of a reflex discharge of adrenergic stimuli which results physiologically from the vertical projection of the long axis of the trunk,[4, 10, 11] and not, as maintained by some,[12, 13] because of changes in the position of the heart. Inasmuch as the stability of the precordial lead T wave in normal subjects is unaffected by such postural change,[4] in contrast with the opposite behavior of the same deflection in the limb leads, the observations, in the present study, of precordial lead T-wave aberrations even during recumbency in cases of "functional" heart disease can be considered not only unique but also of real diagnostic import.

Although the precordial lead T-wave deformities in the cases which formed the basis of the present study have been shown to be due to preponderance of either vagal or sympathetic tone, their resemblance to abnormalities which result from structural cardiac disease is evident. It is for this reason that the interpretation of any distortion of a precordial lead T wave, especially in cases in which the symptoms or signs are merely suggestive of the presence of genuine heart disease, must ultimately depend on a proper assay of these factors. This view is shared, but only in part, by Nordenfelt,[11] for he believes that heightened sympathetic tone alone can cause "functional," spontaneous aberration of a precordial lead T wave, and therefore concludes that any abnormality of this deflection (with the subject recumbent) which is not abolished by a sympatholytic drug, such as ergotamine, shall be construed as indicative of organic heart disease. However, the observations in Cases 1 and 2 suggest the need for extending the concept of the close relationship of autonomic imbalance to "functional" T-wave distortions to include the role of heightened vagal tone, as well.

The testing methods which have been developed in order to permit a proper evaluation of the extent to which an alteration of a precordial lead T wave represents an expression of tonal preponderance of either of the components of the autonomic nervous system are carefully described in the text of this critique. By this means it is possible to attribute to vagotonic influences any aberration of this deflection which is exaggerated by a sympatholytic drug and abolished by parasympatholytic and sympathomimetic drugs or by the assumption of the upright position, whereas an altered T wave which is normalized by a sympatholytic drug and exaggerated by a sympathomimetic drug or the assumption of the upright position can be related to increased sympathetic tone (Table II). Aside from their simplicity and harmlessness, these procedures have been found ideal for the purpose because of the fact that similar T-wave alterations which are due to structural changes remain unaffected by them.[4]

However, even if a deformed precordial lead T wave, by its characteristic responses to these simple procedures, can be properly identified, the cause of the underlying imbalance of the nervous control of the heart needs also to be established. The excessive discharge of adrenergic or cholinergic stimuli which is known to accompany disturbed emotional states in animal experiments[14, 15] suggests that emotional instability may prove to be the dominant factor in the production of such unstable T waves in man. Their frequent occurrence in the cases of neurocirculatory asthenia described in this report would seem to support this view. This opinion is also inferentially corroborated by a critical examination of Nordenfelt's data,[11] which indicates that the "sympathicotonic" T waves which he describes can be correlated with various types of functional disease.

Moreover, spontaneous fluctuations in the form, amplitude, and polarity of a vagotonic or sympathicotonic precordial lead T wave in successive electrocardiograms on the same subject was a characteristic feature in the cases which formed the basis of this study. Since malposition of the exploring electrode was excluded as a causative factor, the likely explanation for this phenomenon is the occurrence of a variation in the degree of autonomic nervous dysfunction arising from variations in the intensity of the emotional disturbance. It is therefore important not to disregard this possibility lest a mistaken diagnosis of acute myocardial change be made, especially when arthralgias, a systolic murmur, and precordial pain are associated manifestations of the syndrome.

It has also been observed that the T-wave representation of autonomic imbalance in the human electrocardiogram may occasionally disappear spontaneously and completely, in both the "vagotonic" and "sympathicotonic" groups (Cases 2 and 4). Under such circumstances, the use of an appropriate drug or maneuver will result in a distortion of

the precordial lead T wave analogous to that which had been apparent in the same case in a routine tracing at a previous time (Case 2, Fig. 6; Case 4, Fig. 8). The implications of this phenomenon are far-reaching. For one thing, it would seem that a dysfunction of the autonomic nervous system can never be entirely dismissed, even when all the electrocardiographic deflections in a single, routine record are normal, unless a "latent" preponderance of the cholinergic or adrenergic components can be excluded by supplemental studies following the administration of sympatholytic or parasympatholytic drugs, respectively. Other advantages in the use of this simple method for the identification, through the medium of the human electrocardiogram, of a "latent" imbalance of autonomic function in man will be more fully dealt with in a subsequent paper.

The relation of heart rate to the appearance or disappearance of aberrant T waves due to excessive adrenergic or cholinergic impulses cannot be stated with finality at this time. Most often, but not always, a "vagotonic" T wave, when it occurred spontaneously, was associated with a relatively slow rate (Table I); when it was exaggerated by ergotamine, it was accompanied by bradycardia; and, when it was abolished by parasympatholytic or sympathomimetic procedures, the influence of cardiac acceleration could not be entirely discounted. On the contrary, the appearance of a "sympathicotonic" T wave was not always associated with tachycardia, and the elimination of such a deformity by ergotamine was not always dependent on the development of bradycardia. In any event, it appears to be true, in the present group, that the occurrence of a bizarre T wave, whether it be due to vagotonia or sympathicotonia, cannot be correlated with a critical heart rate in the same person. The parallelism sometimes seen may be coincidental, in that both are independent effects of nerve tone. The rate, therefore, can be considered only another measure of the degree of nerve tone dominance.

The mechanism by which the precordial lead T wave is as greatly distorted in cases of neurocirculatory asthenia as in instances of structural cardiac disease will require further study. It is possible that the phenomenon may be related to a disturbance of ionic equilibrium in the cellular electrolytes, which is known[16] to result from overexcitation of one or the other components of the autonomic nervous system in response to various emotional stimuli. Conceivably, the summated electromotive forces which are projected in the preterminal deflection of the human electrocardiogram may be sufficiently altered by this means to produce the T-wave changes encountered in these instances. In any case, it can be categorically stated, from the evidence at hand, that the balanced dualistic role of the autonomic nervous system in the preservation of cardiac homeostasis is important not only because of the regulatory control it exercises upon the rate, rhythm, and conduction, but also

because of its modifying influence upon the electrical events which accompany cardiac muscle contraction. The prediction can therefore be ventured that recognition of the contribution of autonomic nervous stimuli to this latter function undoubtedly will prove of assistance in the appraisal of heretofore obscure phenomena in the human electrocardiogram.

SUMMARY AND CONCLUSIONS

1. It is shown that multiple precordial leads derived from the left hemithorax of the recumbent subject suffering from "functional" heart disease may reveal alterations in form, amplitude, and polarity of the T wave which are indistinguishable from those associated with structural cardiac disease.

2. The role of heightened vagal tone or of sympathetic tonal preponderance in the production of these abnormalities of the precordial lead T wave is demonstrated. It is therefore urged that, in the evaluation of any bizarre T wave in the precordial or limb leads when the subject is recumbent, the factor of autonomic imbalance should always be considered.

3. Simple testing methods based on procedures which cause sympathomimetic, sympatholytic, parasympathomimetic, or parasympatholytic effects are described for differentiating these "functional" T-wave alterations from similar changes caused by organic heart disease. It is therefore advocated that these testing methods be applied to every electrocardiogram in order to permit a proper appraisal of any potential or manifest T-wave abnormalities.

4. The demonstration through the medium of the human electrocardiogram of a state of "latent" vagotonia or sympathicotonia is briefly discussed.

5. The instability of these bizarre precordial lead T waves of "functional" origin in successive cardiac cycles in the same electrocardiogram or in successive electrocardiograms in the same case is demonstrated. The importance of recognizing this characteristic feature in the electrocardiograms of persons with "functional" heart disease is emphasized. Methods for avoiding the mistake of attributing these changes to active heart disease are described.

6. The importance of emotional factors in the production of "functional" precordial lead T-wave distortions is stressed.

7. The relation of heart rate to the occurrence or disappearance of these "functional" aberrations of the precordial lead T wave is considered.

8. The mechanism by which vagotonic or sympathicotonic influences can alter the preterminal deflection of the human electrocardiogram is briefly discussed.

9. The importance to the Armed Forces of recognizing these unstable precordial lead T waves, because of their relation to neurocirculatory asthenia, is stressed.

10. Evidence is presented to indicate that the balanced dualistic role of the autonomic nervous system in the preservation of cardiac homeostasis is important not only because of the regulatory control it exercises upon the rate, rhythm, and conduction, but also because of its modifying influence upon the electrical events which accompany cardiac muscle contraction.

11. The timeliness of these observations is evident because the recent recommendations of the American Heart Association for the routine employment of multiple precordial leads was prompted primarily by a desire to increase the usefulness of the electrocardiograph in the diagnosis of structural cardiac disease.

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THE RELATIONSHIP OF BLOOD VISCOSITY TO THE INTENSITY OF HEART MURMURS

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LATE in 1942, a patient with polycythemia was admitted to the New York Hospital. His erythrocyte count was 9,000,000, his hemoglobin, 23.8 Gm. (165 per cent), and his hematocrit, 79 per cent. The bone marrow showed no evidence of polycythemia vera. The electrocardiogram indicated a congenital defect, and the roentgenogram showed a tremendously enlarged pulmonary conus. However, no murmur could be heard. Because of the absence of a murmur, the possibility of polycythemia due to a congenital heart lesion was ruled out. In the light of this interpretation, further observations were indicated to ascertain more precisely the character and extent of the changes in murmurish sounds produced by alterations in the viscosity of the blood.

METHOD

A modification of the Wiggers[1] circulation machine was used. A constant-speed electric motor drove the machine, which was adjusted to pump at a rate of 50 strokes per minute and at a constant stroke volume of 30 c.c. A system of valves prevented backflow, and the circulating medium passed through thick rubber tubing, representing the blood vessels.

Sounds simulating murmurs of cardiac origin were produced by causing blood to pass through a 1 cm. copper tube, closed at one end except for three small openings, each 2 mm. in diameter. This end of the copper tubing was enclosed in a thickwalled rubber tube, 3 cm. in diameter, from which the blood returned to the pump. By this arrangement, turbulence in the flow of blood was produced as it passed through the openings in the copper tubing and into the larger rubber tube. The oscillations so produced in the fluid caused the walls of the rubber tube to vibrate.

A rubber nipple was glued to the 3 cm. tube, just above the three openings in the copper tube. A stethescope or a microphone was fitted into the rubber nipple, forming an airtight seal. By this means the sounds produced were picked up (Fig. 1).

The amplification and recording systems were made up as follows: a microphone was connected to a specially designed amplifier system, which, in turn, was connected to a loud-speaker. The vibrations of the armature of the loud-speaker were transmitted by a thin copper wire to a small mirror. A beam of light from a projector was reflected from the mirror, and recorded by means of a photokymograph. This system was capable of reproducing frequencies up to 500 cycles per second. The murmurs produced had frequencies under 100 cycles per

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second; therefore, the amplifier system was fully adequate to the requirements of this study.

The system was insulated as well as possible against extraneous sounds and electrical fields. Amplification was kept constant.

At all times during the experiments the systolic pressure was kept constant by varying the resistance with a screw clamp beyond the source of the murmur. Since temperature affects the viscosity of blood, it was maintained in these experiments at 20° C.

The circulating medium consisted of Group A bank blood from which most of the plasma had been removed. For the initial observations, blood was used with a hemoglobin level of 140 per cent and an erythrocyte count of 6.9 million. After recordings had been made, the viscosity was lowered, by adding plasma and saline, to 120 per cent hemoglobin, without stopping the circulation in the machine, and with special care not to introduce air bubbles. Thirty minutes were allowed for thorough mixing before taking samples for hemoglobin determination. Recordings of the sounds were then made. This procedure was repeated at hemoglobin levels of 115 per cent, 105 per cent, 90 per cent, and 70 per cent. From ten to thirty sound cycles were recorded and averaged at each level. Additional evidence in corroboration of the observations was obtained by auscultation, and also by increasing the viscosity of the blood through adding more corpuscles.

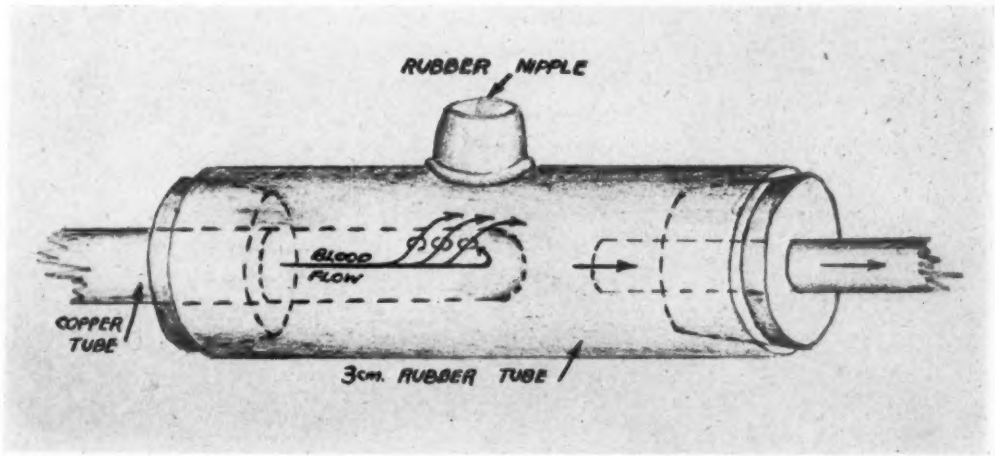

Fig. 1.—Drawing of apparatus used to produce the murmur.

The viscosity of samples of the circulating blood was ascertained by measuring the time taken by 25 c.c. of blood in a filled 50 c.c. burette to pass through a capillary tube, as compared with measurements made in the same way with distilled water.

The criterion used for the intensity of a murmur was the distance from the peak of the fourth highest to the peak of the fourth lowest line in the same records. When this criterion is used, the results of averaging several series of three groups of ten successive murmurs show a deviation of less than 3 per cent for the average of ten cycles. The noise level of the amplifying and recording apparatus was found to be 6 mm., caused by "AC hum" of the radio and electrical interference

of the motor, even when no blood was flowing through the apparatus. This 6 mm. level was therefore the zero point in measuring murmur intensities.

RESULTS

With a hemoglobin level of 140 per cent and an erythrocyte count of 6.9 million, no murmur could be detected, either in the records or by auscultation. At 120 per cent hemoglobin, a very faint murmur was detected by the increased amplitude of the vibration. The murmur

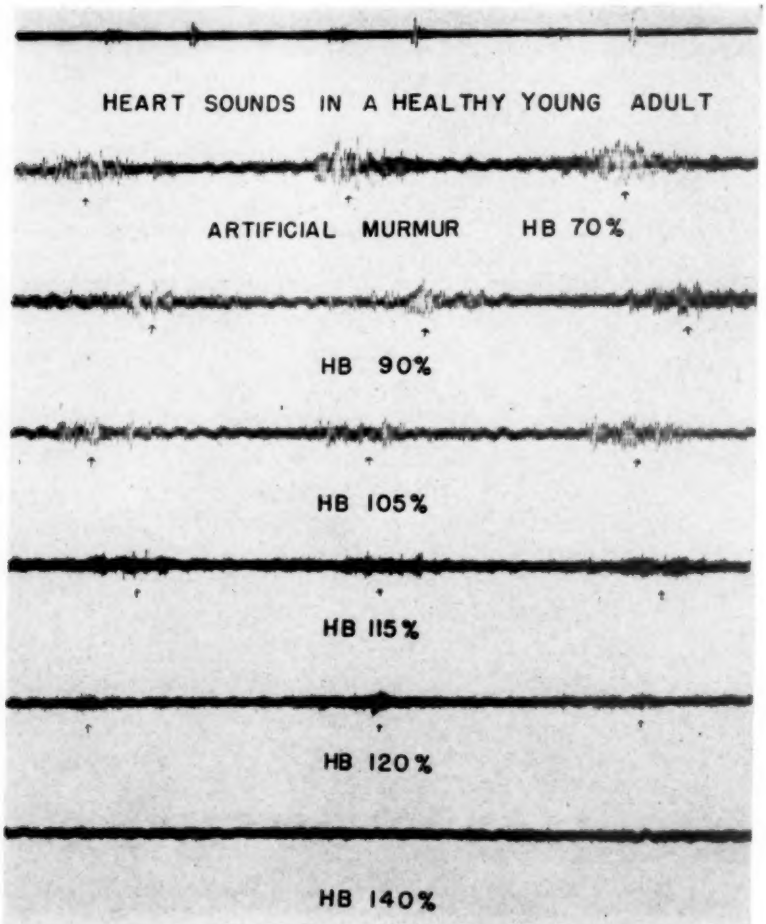

Fig. 2.—Comparison of recordings of normal sounds and artificial murmurs. All recordings are made at the same amplification (×1/3).

grew progressively louder as the blood was diluted, until, at a hemoglobin level of 70 per cent, it was louder than normal heart sounds over the pulmonic area (Fig. 2). Below a hemoglobin level of 70 per cent, no change in the intensity of the murmur could be found. The intensities of the murmurs were measured, tabulated, and plotted.

TABLE I

HEMOGLOBIN LEVEL (%)	MURMUR INTENSITY (MM.)	VISCOSITY
140	6.0	13.5
120	7.6	7.5
115	9.6	6.1
105	12.0	4.1
90	13.4	3.0
70	14.8	2.5

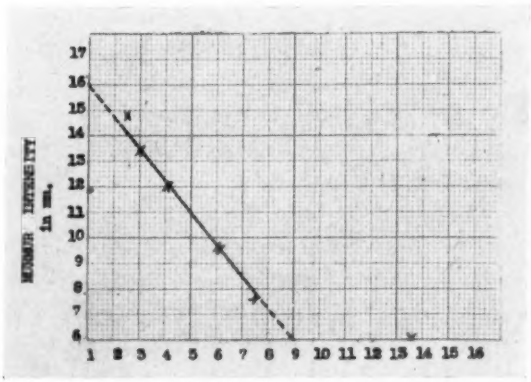

Fig. 3.—A graph of murmur intensity compared to blood viscosity. The dotted line represents the theoretical extension of the graph.

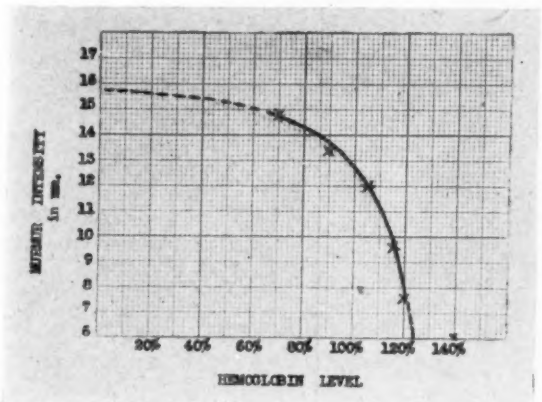

Fig. 4.—A graph of murmur intensity compared to blood hemoglobin content. The dotted line represents the theoretical extension of the graph.

DISCUSSION

Observers agree that murmurs are produced by turbulent blood flow. Hydraulic studies have shown that turbulence decreases with increased viscosity.[2] Since turbulence is the cause of murmurs, one would expect murmur intensity to decrease with increased viscosity. Fig. 3 presents evidence in support of this concept. Although some workers are of the opinion that, below 100 per cent hemoglobin, viscosity is directly related

to the hemoglobin and erythrocyte content,[3] all agree that, at hemoglobin levels over 100 per cent, the relationship of viscosity to hemoglobin is hyperbolic.[3, 4] Since viscosity increases hyperbolically with increased hemoglobin and erythrocyte count, the murmur intensity should drop precipitously with increasing blood hemoglobin levels. Fig. 4 shows that the experimental observations accord with this theory.

Although, for convenience, hemoglobin levels are given in this paper, it should be emphasized that the erythrocyte count is probably more important in determining viscosity. However, since the blood used in this experiment had a color index of one, the use of hemoglobin content is valid.

From Fig. 4, it may be deduced that a murmur heard at 100 per cent hemoglobin should have an amplitude of 13 mm. A murmur heard at 70 per cent hemoglobin measures 14.8 millimeter. The difference is 1.8 millimeter. A murmur 1.8 mm. above the zero point, or 7.8 mm., is slightly louder than the murmur recorded at 120 per cent hemoglobin. The latter is an unmistakable murmur, approximately as loud as the normal first heart sound (Fig. 2). This would indicate that a lowering of blood viscosity is, in itself, enough to bring out a definite murmur, even if the rate of flow and the size of the orifices are constant.

The intensity of the murmur decreased precipitously as the hemoglobin rose over 100 per cent (Fig. 4). At 105 per cent hemoglobin the murmur was louder than normal heart sounds (Fig. 2). At 120 per cent hemoglobin, it became much fainter, and, at 140 per cent hemoglobin, it disappeared completely. Since in both primary and secondary polycythemia erythrocyte counts over 7 million, hemoglobin levels from 125 per cent to 165 per cent, and viscosities of 20 to 32 are expected,[5] it follows that the absence of a murmur in polycythemia does not rule out gross structural cardiac abnormalities. Furthermore, the presence of a murmur in polycythemia probably indicates a much more extensive abnormality than it would if the blood picture were normal.

SUMMARY

1. A method of producing and recording a murmur is described.

2. The murmur produced was found to decrease precipitously with increased blood hemoglobin levels.

3. The results show that lowering of viscosity is, in itself, enough to produce a definite murmur where none was heard before. This may indicate the origin of the hemic murmur.

4. With high blood viscosities, the absence of a murmur does not rule out gross structural cardiac abnormalities.

I am greatly indebted to Dr. Dayton J. Edwards, under whose sympathetic guidance this work was carried out, and to Dr. William Geohegan, who designed and built the amplifying and recording systems.

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ELECTROCARDIOGRAPHIC STUDIES IN NEUROCIRCULATORY ASTHENIA

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NEUROCIRCULATORY asthenia is not uncommonly confused with organic heart disease. In many instances, this is due to misinterpretation of changes in the electrocardiogram and a failure to recognize that the electrocardiogram may be altered at times by this condition. It is important to recognize the true nature of neurocirculatory asthenia to avoid a false diagnosis of organic heart disease and the possibility of engendering cardiac invalidism.

There are conflicting statements in the literature regarding the electrocardiographic findings in neurocirculatory asthenia. A recent editorial[1] states that the electrocardiogram in this condition does not reveal any structural change. Master[2] commented on the slender, asthenic person with a low diaphragm and small heart, and stated that, in a series of thirty cases which he observed, the electrocardiogram was typical. There were small QRS complexes in Lead I and tall QRS complexes in Leads II and III, with an occasional tendency to right axis deviation.

Craig and White[3] reviewed the electrocardiograms of 35 patients with neurocirculatory asthenia. There were 15 instances of sinoauricular tachycardia, 1 instance of auricular premature contractions with bigeminy, 8 instances of diphasic T waves in Lead II, with inverted T waves in Lead III, 6 instances of left axis deviation in obese patients, and 5 instances of a tendency to right axis deviation. In 5 patients there was a history of paroxysmal tachycardia. Graybiel and White[4] reported 7 cases of neurocirculatory asthenia with inversion of the T waves in Leads II and III.

Dry[5] lists the electrocardiographic changes which may occur in neurocirculatory asthenia as follows:

1. Prolonged P-R interval.
2. Prolonged QRS interval, usually with a shortened P-R interval.
3. Sinoauricular block.
4. T-wave changes which affect Leads II and III, or all three standard leads.

Other authors[6] mention elevation of the R-T segments in one or more leads and high voltage of the T wave in Lead I.

It is clear from the literature that there is no characteristic electrocardiogram in neurocirculatory asthenia.

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Among 4,500 patients in the Cardiovascular Section of Lawson General Hospital over a period of two years, there were 150 patients with neurocirculatory asthenia with symptoms severe enough to warrant their seeking medical advice. Numerous other patients with mild symptoms of this condition were seen in routine consultation, but were omitted from this study. A review of the electrocardiograms taken on these patients showed that 49 per cent of them had variations from the textbook normal. The observations in our series of patients are tabulated in Table I.

It is to be noted that the most frequent abnormality was low voltage of less than 1 mm. of the T wave in Lead I, using 1 mm. as the upper limits of normal (Fig. 1, *A*). This occurred in twenty-two, or 14 per cent, of the cases.

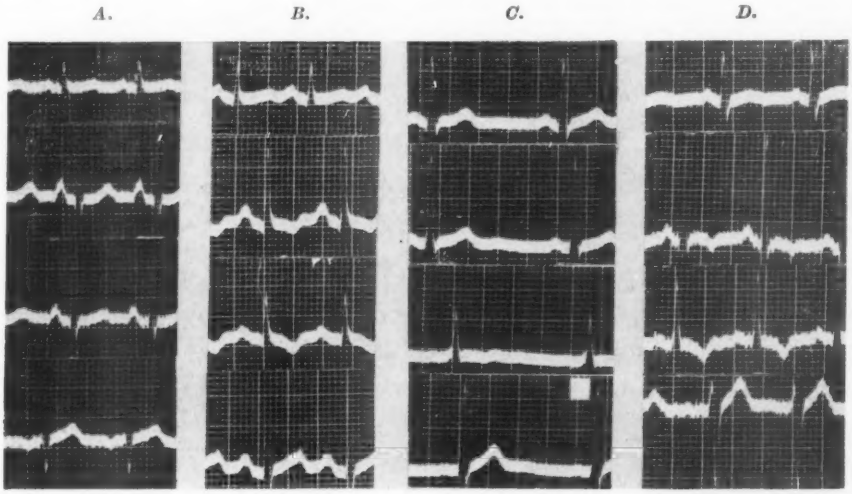

Fig. 1.

There were 6 additional instances in which both T_1 and T_2 were of low voltage. In only 2 instances was the T wave inverted in Lead I. Thus the T wave in Lead I was abnormal in 28, or 20 per cent, of the cases. This was usually accompanied by tachycardia.

There were 18 instances in which the T wave in Lead III was diphasic or inverted, and 9 instances in whch the T waves were inverted in Leads II and III (see Fig. 1, *B*). Thus the T wave was abnormal in Lead III in 27 instances, or 18 per cent of the cases.

The T wave was of low voltage in Lead II in 5 cases and diphasic or inverted in 9 cases, or abnormal in 21, or 14 per cent of the cases.

The P-R interval was prolonged in 7 instances in which there was no evidence of heart disease or history of any disease which might reasonably be associated with prolonged conduction. Atropine in doses of 1/75 grain was given intravenously to four men in this group. In

TABLE I

ABNORMALITIES OF THE ELECTROCARDIOGRAM IN SEVENTY-FOUR CASES OF NEUROCIRCULATORY ASTHENIA

ABNORMALITY	FREQUENCY
Axis deviation, left	14
Axis deviation, right	6
Extrasystoles	6
Intraventricular block, S-wave type	1
P-R interval prolonged	7
Q_3 deep	3
R_4 small	1
QRS slurred all leads	4
S-T elevation	3
S-T depression	1
T_1 inverted	2
T_1 low	22
T_1 and T_3 low	6
T_2 diphasic and inverted	1
T_2 low	5
T_2 and T_3 diphasic and inverted	9
T_2 and T_3 inverted after tilting	12
T_3 diphasic and inverted	18
T_4 inverted	2
T_4 low	2
Low QRS_1, high $QRS_{2 \text{ and } 3}$	35

three cases the P-R interval returned to normal. It was felt that, when there was a response to atropine, prolongation of the P-R interval was due to increased vagal tone.

Extrasystoles were surprisingly infrequent; they were seen in only 6 cases. This is not a true picture, for they are much more common upon physical examination, in our experience, and there is considerable fortuitousness in the recording of these variations.

The type of change described by Master, consisting of a low amplitude of QRS in Lead I with a high amplitude of the QRS in Leads II and III, was seen in thirty-five instances, or 23 per cent of the cases. This variation is related to body build, and is associated with a long, narrow chest and low diaphragm with small heart. In our experience, these changes are not uncommon with this type of physiologic build, and are not believed to be related to the syndrome of neurocirculatory asthenia per se.

There were 12 additional patients whose electrocardiograms were normal in the recumbent position, but who developed inversion of the T waves in Leads II and III upon tilting to 65° on a tilt table (Fig. 1, *C* and *D*). The mechanism of this change is not clear, but it may be associated with a diminished venous return to the heart, with a secondary fall in cardiac output in patients with vasomotor instability. Hyperventilation may at times play a part, as has been pointed out by Thompson,[7] but this condition was not prominent in the present group of cases. These occurred in a series of 50 tilt table tests, with tracings taken immediately before tilting, three minutes after tilting, and twenty minutes after tilting. There were three positive tests, with in-

version of the T waves in Leads II and III in the absence of the clinical picture of neurocirculatory asthenia. Of these, there were two cases of angina pectoris and one of vasomotor instability without subjective symptoms.

There were 20 instances of axis deviation, including 14 cases of left axis deviation and 6 cases of right axis deviation. A tendency to right axis deviation was not uncommon. Other changes were intraventricular heart block of the S-wave type, deep Q_3, small R_4, S-T elevation or depression, and a T wave of low voltage or inverted in Lead CF_4.

The occurrence of alterations of the T waves, including low amplitude of the T wave in Lead I, and low amplitude and inversion of the T waves in Leads II and III, necessitates the differentiation of neurocirculatory asthenia from coronary arteriosclerosis with or without angina pectoris. The differential diagnosis rests upon the history and physical examination, and not upon the electrocardiographic findings. Similar changes may be observed in the electrocardiogram in neurocirculatory asthenia and in coronary arteriosclerosis.

From a brief review of the literature and from the results of this study, it is felt that there is no characteristic electrocardiogram in neurocirculatory asthenia. A number of variations from the normal may be encountered.

SUMMARY

The electrocardiographic variations in 150 patients with neurocirculatory asthenia are presented. A brief review of the literature concerning the electrocardiographic changes in neurocirculatory asthenia is given. The importance of avoiding misinterpretation of confusing electrocardiographic changes as evidence of organc heart disease is emphasized. Alterations in the electrocardiogram similar to those observed in coronary arteriosclerosis may be seen in neurocirculatory asthenia. The differentiation rests upon the history and physical examination, rather than upon the electrocardiogram. There appears to be no characteristic electrocardiogram in neurocirculatory asthenia.

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RUPTURE OF MITRAL CHORDAE TENDINEAE

Clinical and Pathologic Observations on Seven Cases in Which There Was no Bacterial Endocarditis

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MOST of the attention given to rupture of the chordae tendineae of the mitral valve has been accorded those instances which occur during the course of acute or subacute bacterial endocarditis, or which result from severe external violence to the chest. Frew[1] described a case in which rupture of the mitral chordae tendineae took place during a prolonged attack of acute rheumatic fever; and Frothingham and Hass[2] have reported an instance of spontaneous rupture of mitral chordae which were apparently not the site of previous disease.

In the last 2,400 autopsies at the Peter Bent Brigham Hospital, there were eleven instances of rupture of the mitral chordae tendineae. Four were associated with bacterial endocarditis involving this valve. The other seven patients presented no evidence of bacterial endocarditis and no history of severe trauma to the chest, but the mitral valves and their chordae tendineae showed scarring, calcification, or other pathologic changes. It is the purpose of the present report to discuss these instances of spontaneous rupture of scarred or chronically injured mitral chordae tendineae and to correlate the clinical and pathologic characteristics of the syndrome.

REPORT OF CASES

Case 1.—A 51-year-old white woman was first admitted to the hospital in February, 1941, because of shortness of breath of sudden onset three weeks previously. There was no history of rheumatic fever. Ten years before admission the patient was told that she had hypertension, but there had been no symptoms referable to the cardiovascular system. For over three years preceding admission she had been examined by her physician at intervals of two to three months. The systolic pressure had been consistently in the neighborhood of 260 mm. Hg. No cardiac murmurs had been heard. Three weeks prior to admission, after cleaning the cellar, tending the furnace, and lifting and shoveling coal, she climbed the stairs to her kitchen and thereupon became aware of severe, unusual shortness of breath. This subsided after a few minutes. On the following day she went to her doctor. Having examined her heart a month before and found no murmurs, he was

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surprised on this occasion to hear a very loud systolic murmur all over the precordium. The patient was treated with rest and digitalis. Three weeks later she was admitted to the hospital.

Physical examination showed a markedly obese woman who was able to lie flat without distress. The pupils reacted to light. The arteries of the fundus oculi showed thickening and arteriovenous nicking, with several areas of old exudate. The neck veins were not distended. There was moderate, soft enlargement of the thyroid. The heart was enlarged to the left and a strong impulse was noted. No thrill was felt on this admission. There was a harsh, precordial, systolic murmur transmitted into the neck and left axilla, but no diastolic murmur was heard. The rhythm was normal, with a rate of 100 per minute. The blood pressure measured 220/130. The lungs were normal on auscultation. There was slight tenderness below the right costal margin, but the liver could not be felt. No edema was present.

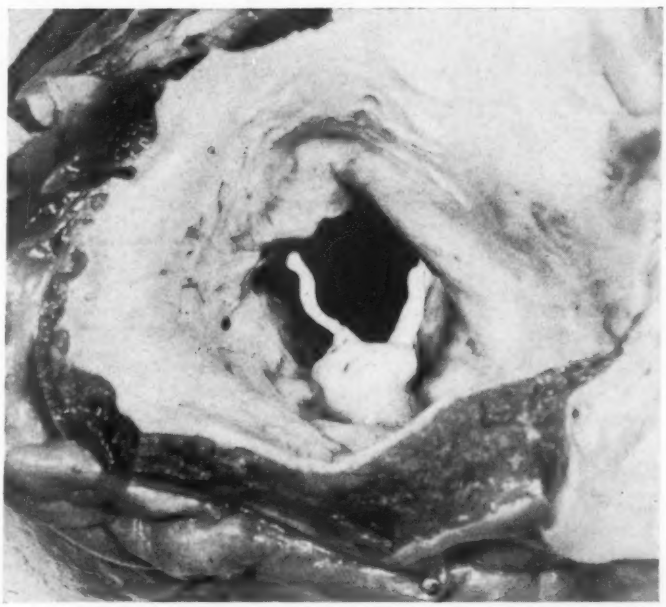

Fig. 1.—Case 1. The atrial surface of the mitral valve. The cusps of the valve were thickened, but there was no significant degree of stenosis. There was considerable ballooning upward of the posterior cusp, from which the ends of two ruptured chordae tendineae projected into the valve orifice. Note the bulbous tips of the free ends of the ruptured chordae tendineae.

The blood Wassermann and Hinton reactions were negative. The vital capacity was 1,400 c.c., and the decholin circulation time was 17 seconds. The electrocardiogram showed left axis deviation. The patient was running a low-grade fever, which was ascribed to her urinary tract infection. This responded to sulfathiazole therapy, and she was discharged, afebrile and asymptomatic, on the thirteenth hospital day.

For eight months she felt fairly well on limited activity. Three weeks before her second hospital admission she exerted herself more than usual, and thereafter developed weakness, dyspnea, and orthopnea. Four days before admission, swelling of the feet and ankles appeared for the first time. She was readmitted to the hospital Nov. 4, 1941.

Physical examination showed a severely ill, perspiring woman, sitting up in bed and gasping for breath. The neck veins were distended up to the mandibles when the patient was in a sitting position. The heart was enlarged to the left. The rhythm was normal, except for occasional dropped beats, at a rate of 120 per minute. At the base a rough, loud systolic murmur was heard. At the apex and extending upward over the precordium, there was an intense systolic thrill and a very loud, blowing, systolic murmur. No diastolic murmurs were heard. The blood pressure was 225/115. There were moist râles throughout both lungs, with signs of fluid up to the fifth rib on the left and the seventh rib on the right. Liver dullness extended three fingerbreadths below the costal margin. There was well-marked edema of the legs. The electrocardiogram was essentially unchanged. A teleoroentgenogram showed only 10 per cent enlargement by height-weight ratio. The aorta was moderately tortuous and the hilar vessels were considerably engorged. There was fluid in both pleural sacs. There was definite dilatation of the left atrium posteriorly, with marked systolic expansion of the atrium, suggesting mitral regurgitation. She was given digitalis and diuretics, and was discharged much improved after nineteen days.

After discharge, the patient did fairly well on limited activity, except for several brief attacks of abdominal pain, distention, and vomiting. With the last of these, on May 31, 1942, she developed circulatory collapse, and was brought to the hospital. She died a few hours after admission.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; fibrosis of mitral valve; cardiac hypertrophy and dilatation; generalized arteriosclerosis; hydrothorax, bilateral; ascites; passive congestion of viscera; aspiration of gastric contents in lung; multiple adenomata of thyroid; chronic cholecystitis; cholelithiasis.

The heart weighed 520 grams. The left atrium was considerably dilated, and the right atrium and ventricle somewhat less so; the left ventricle was dilated very little. The right ventricular myocardium measured 0.9 cm. in thickness, and that of the left ventricle, 2.2 centimeters. It was deep red in color and no areas of scarring were found. The tricuspid, pulmonary, and aortic valves were normal in size and texture. A few thrombi were found on the surface of the endocardium just beneath the aortic valve, but elsewhere the endocardium was smooth.

As seen from the atrial surface, the mitral valve was thickened and irregular, but there was no significant degree of stenosis. The ends of two ruptured chordae tendineae projected into the valve orifice from the posterior cusp (Fig. 1). The right portion of the posterior cusp was displaced upward into the atrium. The ruptured chordae were thickened and had rounded free ends. On a papillary muscle of the right group there were two rubbery, rounded elevations, each 2 mm. in height. These represented the original attachments of the ruptured chordae; the rupture had occurred just above the site of attachment. There was considerable atrophy of this papillary muscle, but the other papillary muscles were normal.

There was a moderate degree of sclerosis of the coronary arteries, but they were not occluded or thrombosed. The pericardial sac was normal.

Microscopic Examination.—There was a large amount of dense, hyaline, fibrous tissue in the mitral valve, especially in the central portions of the cusp. Small and large blood vessels were found in all parts

of the mitral cusps. No Aschoff bodies were seen. The stumps of the ruptured chordae tapered at their free ends, and the surfaces were everywhere covered by endothelium. Within the ruptured chordae, the tissue was dense and hyaline, with few cells and blood vessels. The papillary muscle at the point of attachment of the ruptured chordae showed considerable scarring (Fig. 2).

There was edema of the interstitial connective tissue of the myocardium. The myocardium was not otherwise remarkable.

Fig. 2.—Case 1. Photomicrograph of the stump of a ruptured chorda tendinea attached to a papillary muscle. Hematoxylin and eosin stain; magnification, ×75 reduced.

CASE 2.—A 52-year-old white man was admitted to the hospital March 30, 1940. He gave no history suggesting rheumatic fever. Physical examination twenty-five years before was said to have been negative. Sixteen years before admission, during an exhausting struggle in quicksand, he experienced a severe, pressing pain over the heart. For one or two years before admission he had had a similar pressing pain to the left of the sternum on hurrying, particularly in a cold wind. For about three years there had also been shortness of breath on inclines or when running, and palpitation at various times. On the night before admission, the patient was awakened from sleep by a pressing pain in the left side of the chest anteriorly. He was extremely breathless on awakening, and this persisted until he found partial relief by sitting up. On the next day he was admitted to the hospital.

Physical examination showed an obese man, propped up in bed, breathless, weak, pale, moderately cyanotic, perspiring, and cool over the extremities. The temperature was 102° F. (rectal), the pulse rate, 140 per minute, and the respirations, 36 per minute. The heart was enlarged to the left and to the right. There was a diffuse apex impulse, but the radial pulse was noted to be small. On this and all subsequent examinations a coarse, loud, systolic murmur was heard over the precordium, maximal at the apex and along the left border of the sternum; this was accompanied by a systolic thrill. On the first exam-

ination, and irregularly thereafter, a low-pitched diastolic murmur was heard at the apex. The apical first sound was loud and snapping, and the pulmonary second sound was markedly accentuated. The rhythm was normal and the blood pressure was 100/80. Examination of the lungs showed moist inspiratory râles at both bases, inspiratory râles at the left apex, and râles in both phases of respiration at the right apex. The abdomen was moderately distended; the liver was not palpable. The peripheral arteries were in good condition. There was no edema.

The blood Hinton and Wassermann reactions were negative. The electrocardiogram on admission showed sinus tachycardia, left axis deviation, occasional premature ventricular beats, and a normal Lead IV. Four subsequent electrocardiograms showed no essential change except for a digitalis effect. On May 8, the electrocardiogram showed auricular fibrillation. A roentgenogram on April 4 showed cardiac enlargement to the left and right, with a straight left border. There were coarse mottling of both lungs and partial consolidation of the right upper lobe. On April 9 the roentgenogram showed clearing of the lungs, revealing a fine, diffuse fibrosis in the right upper lobe. A third roentgenogram, on April 22, showed no essential change.

At first there was moderate symptomatic improvement. Scattered râles continued to be present over both lungs, particularly at the bases. Repeated examinations of the heart showed some variation in the intensity of the murmur and thrill. On several occasions systole was forcible enough to rock the chest, and there was a wide, lifting, apex impulse. At the same time the peripheral pulse was small. By the third week, signs of fluid appeared in both pleural sacs, more on the left; ascites developed; the liver was felt 3 cm. below the costal margin; the spleen was palpable and firm; and fullness of the neck veins was noted. On April 24 the venous pressure was 260 mm. of saline (normal, 100 mm.). The vital capacity diminished from 1,700 c.c. in the first week to 1,100 c.c. during the third week. On May 14, abdominal paracentesis yielded 1,200 c.c. of yellowish, cloudy fluid with a specific gravity of 1.010. By this time the edema had progressed to involve the lower portion of the body as far up as the nipple line. Auricular fibrillation developed on the fortieth hospital day and persisted until death. The patient became steadily weaker, developed incontinence of urine and feces, and died on the fifty-third hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; fibrosis of mitral valve; myocardial fibrosis; cardiac hypertrophy and dilatation; passive congestion of viscera; thrombosis of branches of pulmonary arteries and veins; acute bronchopneumonia; hydrothorax, bilateral; ascites.

The heart weighed 470 grams. In situ, the heart was considerably dilated, especially the left atrium, and the left ventricle to an only slightly less degree. The cusps of the mitral valve were thickened, but there was no stenosis. The free edges were rolled, and numerous small, firm, white nodules were present on the atrial surface and along the annulus fibrosus of the anterior cusp. The chordae tendineae attached to the left papillary muscle and those extending from the right papillary muscle to the posterior cusp were thickened but intact. Eight chordae tendineae, which originally connected the anterior cusp and the right papillary muscle, were ruptured near the point of attachment to the papillary muscle (Fig. 3). Their free ends were tapered and rounded.

One ruptured chorda was approximately five times the thickness of the others. The portion of the right papillary muscle to which these chordae tendineae were originally attached was atrophic, in contrast to the other portion and the left papillary muscle, which were markedly hypertrophied and which deviated in the direction of the anterior cusp. The aortic, pulmonary, and tricuspid valves were normal. Small nodules similar to those on the mitral valve were present on the intima of the aorta near the orifices of the coronary arteries and on small areas of the endocardium of the right and left atria.

The myocardium was not remarkable. There was slight atheroma of the coronary arteries, but no occlusions were found. The pericardium was normal. Small Soldier's plaques were seen on the epicardium.

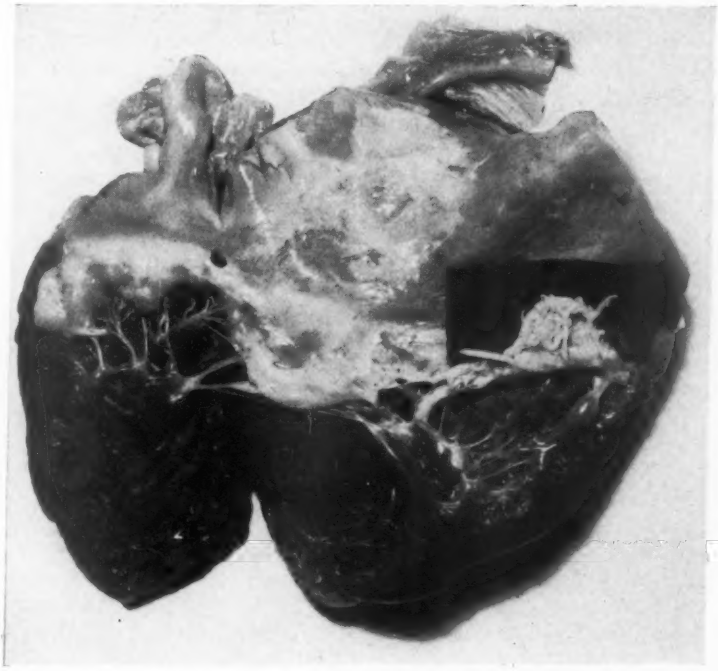

Fig. 3.—Case 2. The anterior cusp of the mitral valve was turned back. Eight chordae tendineae were ruptured, not all of which are shown in the photograph. Note the thickening of the chordae tendineae, the atrophy of the papillary muscle to which the ruptured chordae tendineae had originally been attached, and the hypertrophy of the papillary muscle with intact chordae tendineae.

Microscopic Examination.—The nodules described grossly were composed of dense, hyalinized, connective tissue covered by endothelium. The ruptured chordae were made up of dense, relatively acellular, connective tissue, with basophilic areas of degeneration. Endothelium covered the surface. There was dense connective tissue thickening of the mitral valve. A myocardial vein contained an organizing thrombus. There was a moderate increase in the connective tissue of the myocardium, but no Aschoff bodies or areas of infarction were encountered.

Case 3.—A 54-year-old colored man was admitted to the hospital May 28, 1942. There was no history of rheumatic fever. Five or six

years before admission he had been told that he had high blood pressure, but his only complaint had been occasional attacks of mild epistaxis. Seventeen months before admission, while shoveling coal, he had a sudden attack of dyspnea which lasted for approximately forty-five minutes, during which time he was forced to sit still in an upright position. Thereafter, he had occasional, milder attacks which came on during the course of moderate exertion, but never at night. Usually he was able to discharge his duties without difficulty.

Seven months before admission he began to have a productive cough. Two months later he had the first of several attacks of sharp pain in the anterior part of the chest, apparently accompanied by dyspnea, which sometimes lasted over an hour. Gradually he developed troublesome shortness of breath on exertion, and, six weeks before admission, his physician prescribed a compound of squill, digitalis, and calomel, with moderate improvement. On the day before admission, while walking on the street, he became aware of increasing difficulty in breathing, profuse sweating, and a sensation of abdominal distention. This passed off after an hour, but he coughed up small quantities of bright red blood. On the following day there was a similar attack of dyspnea, because of which he was admitted to the hospital.

For approximately six months before admission he had been under the observation of a physician who had examined him on several occasions. Each time a loud systole murmur had been present. His doctor was under the impression that there had been no change in the character of this murmur.

Physical examination showed a lean, tired, orthopneic Negro, perspiring over the forehead. There were some narrowing of the arteries of the fundus and moderate arteriovenous nicking. A few hemorrhages were seen in the right eye ground, and some exudate in both. The peripheral arteries were thickened and tortuous. The blood pressure was 155/95; later it rose to 190/100. The neck veins were not distended. The heart was enlarged to the left. There were a heaving apical impulse and an apical systolic thrill. The rhythm was normal except for occasional extrasystoles. The rate was 100 per minute. There was a very loud, harsh, systolic murmur, maximal at the apex, but also heard over the precordium and posterior part of the chest. The lungs were normally resonant. There were moist râles at the bases of both lungs and over the upper portion of the right lung, posteriorly. The liver and spleen were not palpable. Slight edema of the ankles was present.

The blood Hinton and Wassermann reactions were negative. The decholin circulation time was fifteen seconds, and the venous pressure measured 40 mm. of saline. Roentgenograms showed marked cardiac enlargement, with a round, blunt left ventricle and a tortuous aorta. There was marked consolidation around the hila of both lungs, with complete consolidation of the right upper lobe. The electrocardiogram showed right bundle branch block.

While in the hospital there were numerous attacks of paroxysmal dyspnea and the chest became filled with râles. The patient failed steadily and died on the seventh hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve, old and recent; endocardial vegetations, organized; cardiac hypertrophy and dilatation; myocardial fibrosis; arteriosclerosis, generalized; pulmonary edema with hemorrhage; thrombosis of branches of pulmonary artery and vein from left lower lobe.

The heart weighed 860 grams. As studied in situ, the heart was very much enlarged, especially the left ventricle, which was larger than the three other chambers combined. As the mitral valve was viewed from above, the anterior cusp was found to be displaced upward (Fig. 4). The free ends of the ruptured chordae tendineae could be made out through the orifice. There were numerous small, grayish-white, soft masses on this cusp, as well as on the endocardium of the left ventricle and on the posterior leaflet of the aortic valve. All the ruptured chordae tendineae belonged to the group attached to the right papillary muscle, on which small nodules represented the ends of the ruptured chordae. There was moderate atrophy of this papillary muscle. The cusps of the mitral valve were thickened and their edges rolled, but there was no stenosis.

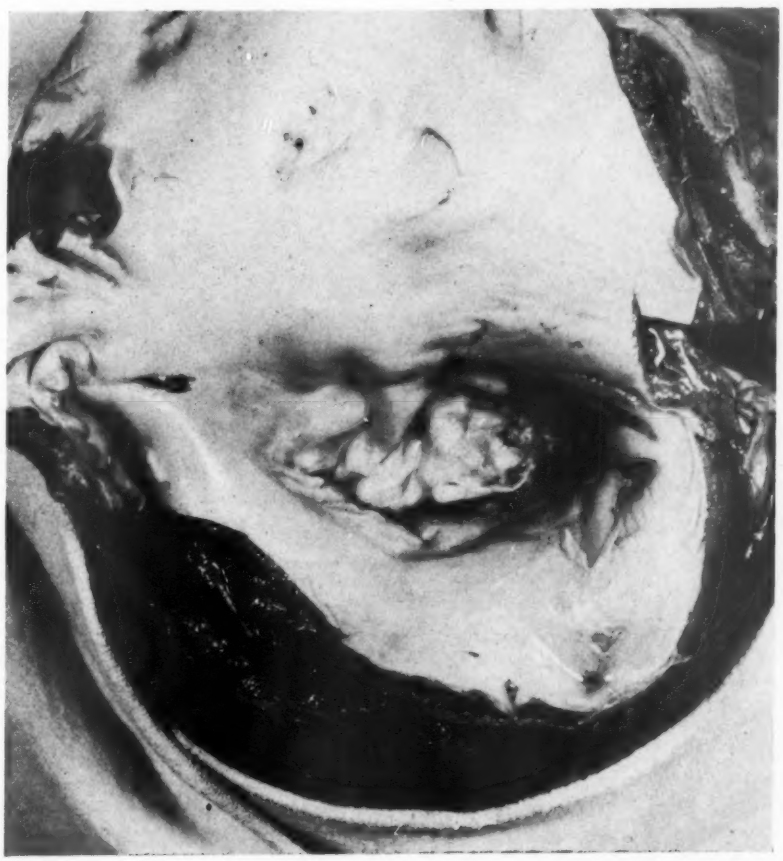

Fig. 4.—Case 3. The anterior cusp of the mitral valve was ballooned upward. The ruptured chordae tendineae are not shown in the photograph.

The left ventricular myocardium measured 3.2 cm. in greatest thickness; and the right, 1 centimeter. There were no areas of scarring. Moderate sclerosis was present in the coronary arteries, but no areas of occlusion or thrombosis were found. The pericardium and epicardium were not remarkable.

Microscopic Examination.—The ruptured chordae tendineae were composed of dense, hyaline, connective tissue, with basophilic degenera-

tion and a few areas of calcification (Fig. 5). Occasional mononuclear phagocytes and rare polymorphonuclear leucocytes were found near the free ends. The mitral valve was irregularly thickened because of increase in hyaline connective tissue, but there was little vascularization. On the surface there were several nodular excrescences composed of dense, collagenous tissue arranged in irregular lamellae. There was no inflammatory cellular infiltration. The masses noted grossly were platelet thrombi without organization; no bacteria were demonstrated.

Sections through the ends of the chordae tendineae attached to the papillary muscle showed two processes. One of these was the presence of very dense hyaline connective tissue, with small areas of calcification;

Fig. 5.—Case 3. The free end of a ruptured chorda tendinea. The surface was completely endothelialized, indicating that the rupture had taken place a long time before death. Numerous areas of calcification are shown. Eosin-methylene blue stain; magnification, ×150 reduced.

this extended into the subjacent myocardium for a short distance (Fig. 6). The other process was characterized by the formation of fresh thrombi on the surface. There were a few mononuclear cells and polymorphonuclear leucocytes in these regions, and in and about some degenerating muscle fibers beneath the thrombi. There was a moderate increase in the interstitial connective tissue of the myocardium. No areas of infarction or Aschoff body formation were found.

In comment, the histologic observations indicated that the chordae tendineae had ruptured on two occasions: on one occasion, a long time before death, and, on the other, a few days before death. The thrombi were evidently formed at the time of, or after, the rupture of the second group of chordae tendineae. There was no evidence of bacterial endocarditis.

CASE 4.—A 78-year-old white farmer entered the hospital Feb. 6, 1938. He had had occasional attacks of tonsillitis, and, in his early twenties, had intermittent fever, requiring over four weeks' bed rest. At the age of 17 years he consulted a physician because of sharp, precordial, nonradiating pain of several weeks' duration. At this time he was told that he had heart disease. At the age of 50 years there was a recurrence of this pain, again of short duration.

Fig. 6.—Case 3. Fibrosis and calcification in a papillary muscle at the site of previous attachment of a ruptured chorda tendinea. Hematoxylin and eosin stain; magnification, ×150.

Fifteen years later he noted recurrence of sharp pain in the precordium and lower substernal region, this time upon exertion. For some years before admission he had noted weakness, easy fatigue, and intermittent swelling of the ankles. Two months before admission he fell, striking the anterior part of his chest. At about this time he began to be extremely short of breath on exertion, and developed persistent swelling of the ankles. A constant aching sensation appeared in the epigastrium associated with slight nausea. Four weeks before admission he consulted a physician, who prescribed digitalis.

Physical examination revealed a somewhat undernourished, elderly man with a malar flush. The temperature was 98.6° F., the pulse rate, 90 per minute, and the respirations, 26 per minute. The vessels

of the fundi showed slight changes in caliber. The radial pulses were equal, regular, and full; the dorsalis pedis pulsations were present. The heart was enlarged to both left and right. On admission the rhythm was normal; on subsequent examinations it was coupled. There were a rough, loud, precordial, systolic murmur, maximal at the apex, and a harsh mid-diastolic apical murmur. Both murmurs, which showed some variation in intensity, were accompanied by thrills. The blood pressure was 150/90. At the bases of both lungs there were numerous moist râles. A firm, tender, liver edge was felt two fingerbreadths below the right costal margin. The spleen was not palpable. There was moderate edema of the legs.

Fig. 7.—Case 4. Calcification in the free end of a ruptured chorda tendinea. Hematoxylin and eosin stain; magnification, ×150 reduced.

The blood Hinton and Wassermann reactions were negative. The vital capacity was 1,800 cubic centimeters. The nonprotein nitrogen of the blood was 117 mg. per 100 c.c. on the sixth day. The electrocardiogram showed delayed A-V conduction and coupled beats.

The patient grew progressively worse, and death occurred on the eighth hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chordae tendineae of mitral valve; rheumatic heart disease; cardiac hypertrophy and dilatation; hydrothorax, right; passive congestion of viscera; edema, generalized; hyperplasia of prostate.

The heart weighed 420 grams. The mitral valve presented a firm nodular thickening of its free edges, especially on the posterior cusp. In the center of the anterior cusp there was an area of calcification measuring 1.5 by 0.5 cm.; another area of calcification, 1.5 by 1 cm., was located at the left lateral angle between the cusps; and a third, 2.5 by 1.5 cm., was present in the posterior cusp. The chordae tendineae were moderately thickened and shortened. Two chordae tendinae were ruptured, one belonging to the middle group of the posterior cusp and the other to the middle group of the anterior cusp. The papillary muscles of the left ventricle were hypertrophied. There was some thickening of the annulus fibrosus of the aortic valve, and fenestration was present along the free edge of its posterior leaflets. The other valves were not remarkable. The chambers of the heart were dilated to about the same degree. The firm, reddish-brown myocardium measured 1.6 cm. in thickness in the left ventricle, and 0.6 cm. in the right ventricle. There were no changes in the endocardium. Moderate sclerosis of the coronary arteries was present, most marked near their orifices.

Microscopic Examination.—The connective tissue of the mitral valve was somewhat increased in amount, and in some areas was more cellular than usual. There were no recent vegetations. The ruptured chordae were composed of very dense, hyalinized connective tissue, with areas of calcification and iron deposit. The free ends were rounded and covered by endothelium except for one point, where a deposit of calcium was covered by an unorganized thrombus (Fig. 7). The papillary muscles at the points of attachment of the ruptured chordae were extensively altered by increase in connective tissue. Near the stump of one of the ruptured chordae there was an area of calcification with a small amount of metaplastic bone formation. In the rest of the myocardium there were a few small areas of connective tissue proliferation, with loss of muscle cells. Most of it, however, was edematous but otherwise normal.

Case 5.—A 71-year-old white garage man was admitted to the hospital Sept. 6, 1934. There was no history suggesting rheumatic fever. He had had chronic bronchitis for twenty years. For a year before admission there had been some shortness of breath on exertion, and for four to five months he had been frequently awakened by shortness of breath, forcing him to sit up. Some five months before admission he first noted swelling of the ankles. Pills, given by his physician, brought only moderate relief. For the last month there had been severe dyspnea, orthopnea, frequent attacks of paroxysmal dyspnea, and massive edema of the legs. He had had profuse sweating. In the few days preceding admission, he had been confused and drowsy.

Physical examination showed an obese elderly man with marked dyspnea, orthopnea, and cyanosis of the face and hands. The vessels of the fundi were obscured by opacities. There were moderate thickening and tortuosity of the peripheral vessels. The pulse was very small in volume, and the apex impulse could not be made out. The heart was enlarged to both left and right. The sounds were irregular and faint; there was a blowing systolic murmur, loudest at the apex of the heart, but also heard over the base, which varied in intensity on successive examinations from moderate to loud. The heart rate was 60 per minute, and the radial pulse rate was 30 per minute. The

blood pressure measured 180/90. At the base of the right lung there was flatness to percussion, with absent tactile fremitus and breath sounds. A few basal râles were heard. The abdomen was somewhat distended. Liver dullness extended 4 cm. below the right costal margin; the spleen was not palpable. There was massive edema over the ankles, legs, and sacrum.

The blood Hinton and Wassermann reactions were negative. The electrocardiogram showed left axis deviation, auricular fibrillation, and occasional ventricular extrasystoles.

The temperature on admission was normal, but in the following days it varied between 100° F. and 102° F. The heart rate ranged between 50 and 80 per minute. The patient failed rapidly, lapsed into coma, and died on the third hospital day.

Necropsy.—Anatomic Diagnoses: Rheumatic heart disease; mitral stenosis and insufficiency, rupture of chordae tendineae of mitral valve; cardiac hypertrophy and dilatation; hydrothorax, bilateral; edema of ankles; pulmonary thrombosis, recent; pulmonary emphysema.

The heart weighed 780 grams. The cusps of the mitral valve were fibrosed and calcified to such as extent that they formed a horizontal shelf with a slitlike orifice at the center which measured 1.5 by 0.7 centimeters. Although the annulus fibrosus measured 9 cm. in circumference, the orifice measured 5.3 centimeters. Three chordae tendineae of the anterior cusp were ruptured, and the free ends attached to the valve were 5 to 6 mm. in length. One of the ruptured chordae had a pointed end; the other two, bulbous tips. The portions attached to the papillary muscle were found in only one case; the fragment measured 3 mm. in length. The unruptured chordae tendineae varied from 1 to 1.5 cm. in length. Some were normal, but others were distinctly thickened. There were no bacterial vegetations. The papillary muscles were slightly hypertrophied. Slight puckering and adherence of the left anterior and the posterior leaflets were the only evidence of disease of the aortic valve. There was some dilatation of the tricuspid valve, but no fibrosis or alteration of the chordae tendineae. The pulmonic valve was normal.

There was marked dilatation of all the chambers of the heart. The left atrium had a capacity of approximately 125 c.c., and the right considerably more. The endocardium was slightly thickened in the left ventricle and normal in the right. The left ventricular myocardium measured 1.6 to 1.8 cm. in thickness, the right, 0.5 to 0.7 centimeters. It was reddish-brown in color, with some grey patches. The coronary arteries showed numerous atheromatous patches without occlusion or thrombosis.

Microscopic Examination.—The mitral valve was greatly thickened as a result of an increase in connective tissue. In part, the connective tissue was cellular, but most of it was dense and hyalinized. There was extensive vascularization of the valve, but no recent vegetations were encountered. The ruptured chordae were not sectioned. The myocardial fibers were large. Occasional small areas of scarring were seen, but there were no Aschoff nodules or infarctions. The coronary arteries showed considerable atherosclerosis without occlusion. There was considerable fibrosis of the epicardium, with some lymphocytic infiltration. The endocardium was not remarkable.

CASE 6.—A 48-year-old white man was admitted to the hospital April 24, 1931. There was no history of rheumatic fever. When he was in the hospital because of a ruptured appendix nine years previously the heart was normal. One year later he was told that he had a "leaking valve." In the two years before admission, shortness of breath on exertion appeared. Six months later he became aware of irregularity and rapid rate of the heart, which were at first intermittent and later constant. For four months there had been a productive cough, insomnia, orthopnea, and nocturia. Nevertheless, he continued to be active and to work until a week before admission, when dyspnea became marked.

On physical examination the patient was a well-nourished, middle-aged, alert white man who was sitting up in bed. His hair was damp, and there was marked perspiration on the forehead and in the axillae. Moderate cyanosis was present in the nail beds of the fingers and toes. The radial and dorsalis pedis pulses were equal. There was marked cardiac enlargement to left and right. The rhythm was totally irregular, with an apical rate of 129 per minute and a radial rate of 66 per minute. A loud systolic murmur was present over the precordium, and a slight systolic thrill was felt in the apical region. No diastolic murmur was heard. The blood pressure measured 134/86. There were slight dullness and a few râles at the bases of both lungs, more on the left. The edge of the liver was palpated 5 cm. below the right costal margin, but the spleen could not be felt. There was slight, nonpitting edema of the ankles.

The blood Hinton and Wassermann reactions were negative. Roentgenograms showed considerable cardiac enlargement, to both left and right, with the left ventricle prominent downward and to the left. In each costophrenic angle there was a small amount of fluid. The lungs were slightly congested. The electrocardiograms showed auricular fibrillation and left axis deviation.

On digitalization, fluid restriction, and diuresis with theocin, the patient improved. However, on the twenty-third hospital day the temperature, which had shown an occasional fluctuation up to 100° F., began to rise, and varied for the last five days between 102° F. and 104° F. The pulse rate slowly rose to 110 to 120 per minute, with a slight deficit. During this time, the respirations varied between 25 and 40 per minute. The leucocyte count rose to 20,000 per cubic millimeter. There were no changes in the pulmonary or cardiac signs. Gradually he became weaker, lapsed into coma, and died on the thirtieth hospital day.

Necropsy.—Anatomic Diagnoses: Rupture of chorda tendinea of mitral valve, old; fibrosis and calcification of mitral valve; cardiac hypertrophy and dilatation; pulmonary thrombosis, recent, bilateral; infarction of liver and kidney; chronic passive congestion of liver; arteriosclerosis, generalized; chronic cholecystitis; cholelithiasis.

The heart weighed 560 grams. On examining the mitral valve from above, the posterior cusp was found to balloon up toward the atrium. Both cusps were slightly but diffusely thickened, and there were a few calcified nodules at the base of the posterior cusp. The orifice, however, admitted three fingers readily. Further inspection from below showed that one of the chordae tendineae of the posterior cusp was ruptured. The portion attached to the cusp was shortened and thickened. The site of attachment to the papillary muscle was rep-

resented by a small fibrotic area without evidence of recent reaction. In addition, there was a fibrous cord between the inferior surface of the posterior cusp and the ruptured chorda tendinea. The unruptured chordae tendineae were thickened and somewhat lengthened. There was slight dilatation of the tricuspid valve, but the cusps were normal. The pulmonic and aortic valves were not remarkable.

All chambers of the heart were dilated. The left ventricular myocardium measured 2 to 2.5 cm. in thickness, the right, 0.3 to 0.4 centimeters. It was deep pinkish-brown in color and flabby in consistency. There was moderate coronary sclerosis without occlusion of any of the arteries. The pericardial sac was normal.

Microscopic Examination.—There were small areas of scarring in the myocardium about medium-sized arteries. Some edema and fatty infiltration of the myocardium were also present. No Aschoff nodules or regions of infarction were present. There was considerable atheroma of a large coronary artery. The epicardium and endocardium were not remarkable. The mitral valve and chordae tendineae were not sectioned.

CASE 7.—A 78-year-old white man was admitted to the hospital July 10, 1930. He had had frequent nosebleeds as a boy, and one attack of tonsillitis many years before. In 1924, he underwent prostatectomy for hyperplasia of the prostate. At that time a systolic murmur was heard over the precordium. The blood pressure measured 130/85. He was again admitted, in 1929, for treatment of a duodenal ulcer which had been diagnosed roentgenologically. In the preceding years he had four attacks of hematemesis following epigastric pain. Examination at that time showed a harsh, loud, systolic murmur over the whole anterior part of the chest, transmitted halfway down to the umbilicus. The apex impulse was not seen or felt. The blood pressure measured 116/76. After discharge, he did well until about ten weeks before admission, when he began to experience considerable dyspnea on exertion, was forced to sleep propped up in bed, and developed a productive cough. Eight weeks before admission he began to sleep sitting up in a chair, and developed edema of the ankles which extended up the legs, at times even involving the lower part of the thighs. The attacks of dizziness and palpitation which he had had for years became more severe. Occasionally the patient experienced some pain in the chest.

Physical examination showed a fairly well-preserved, but confused, elderly white man in considerable respiratory distress. There were a malar flush and moderate cyanosis of the face, lips, tongue, and nail beds. The arteries of the fundus oculi showed slight arteriovenous nicking and diminution in caliber. There were considerable tortuosity and thickening of the peripheral vessels. A diffuse apex impulse was visible and palpable 11 cm. to the left of the midsternal line in the fifth intercostal space. There was a systolic thrill at the apex and in the third and fourth intercostal spaces. The heart sounds were of fair quality. The rhythm was normal. A loud, high-pitched, rather harsh, systolic murmur was heard all over the precordium, but loudest at the apex. No diastolic murmur was heard. The blood pressure measured 140/100. Moist and crackling râles were present at the bases of both lungs posteriorly up to the inferior angles of the scapulae. The liver and spleen were not palpable. There was considerable edema of the lower thirds of both legs.

The blood Wassermann and Hinton reactions were negative. The electrocardiograms showed left axis deviation.

While in the hospital the patient was restless and disoriented. The pulse rate rose steadily to 120 per minute. There was Cheyne-Stokes breathing, with periods of apnea lasting up to forty seconds. Incontinence of urine and feces developed, and, during the last two days, dark-red blood was passed by rectum. Death occurred on the eighth hospital day.

Necropsy.—Anatomic Diagnoses: Gastric ulcers, multiple; hemorrhage into gastrointestinal tract; bronchopneumonia; fibrinous pleuritis, right; anomaly of mitral valve; rupture of chordae tendineae of mitral valve; arteriosclerosis, generalized; chronic passive congestion of liver.

The heart weighed 450 grams. When the atrial surface of the mitral valve was inspected, the posterior cusp was found to bulge upward into the atrium. The orifice admitted three fingers. Both cusps were thickened and fibrosed, but not calcified. Inspection from below showed that all the chordae tendineae were shortened and thickened. Those of the anterior cusp were attached by a meshwork of fibers, not only along the margins of the cusp, but also for 2 cm. toward the annulus fibrosus. None was ruptured. The chordae tendineae of the posterior cusp were inserted by a similar network of interlacing fibers over the entire undersurface of the cusp. From this network the usual number of thick chordae tendineae extended to the papillary muscles. Three of the chordae tendineae of the posterior cusp were ruptured. The stumps of two of these were found on the papillary muscles. The papillary muscles were markedly hypertrophied. The only abnormality of the aortic valve was slight thickening and calcification of its free margins. The tricuspid valve was somewhat dilated; the pulmonic valve was normal.

There was dilatation of all the chambers of the heart, but predominantly of the left ventricle. The coronary arteries were tortuous, but showed minimal arteriosclerosis. The left ventricular myocardium measured 1.6 cm. in thickness, the right, 0.3 to 0.4 centimeters. It was pinkish-brown; no areas of scarring were found. The pericardium was not remarkable.

Microscopic Examination.—There were a few small areas of scarring about thickened arterioles of the myocardium, and a small amount of fat tissue was seen between some of the bundles. Elsewhere, the myocardial fibers were somewhat larger than normal, but otherwise were well preserved. The epicardium was not remarkable. The mitral valve and ruptured chordae tendineae were not sectioned.

DISCUSSION

Each of the seven patients discussed in this paper presented evidence of rupture of the mitral chordae tendineae. None had acute or subacute bacterial endocarditis. In each case disease of the valve and its chordae tendineae appeared to antedate the rupture.

The chordae tendineae of the left ventricle arise from two groups of papillary muscles, the medial, or posterior, and lateral, or anterior, and insert, respectively, in the posterior and anterior halves of the mitral valve cusps. They serve the function of checking the cusps during ventricular systole so that the valve closes efficiently under normal circumstances. Their rupture allows the affected portion of the cusp to balloon up into the atrium, leaving a gap through which blood regurgitates during systole.

It is difficult to state with assurance in most instances what was the nature of the disease of the mitral valve and its chordae tendineae antedating the rupture. In some, rheumatic fever was the antecedent disease. There was a history suggestive of rheumatic fever in Cases 4 and 7. At necropsy, the lesions in Cases 4 and 5 were those of rheumatic heart disease with involvement of the mitral valve and its chordae tendineae. In the other cases there was fibrosis of the mitral valve without stenosis. The chordae tendineae were thickened as the result of increase in connective tissue; this connective tissue occasionally showed degeneration, and, in Cases 3 and 4, calcium deposits. No sections of chordae tendineae were taken in Cases 5, 6, and 7. These lesions more nearly resembled quiescent rheumatic disease than any other type of involvement of these structures. However, there were no pathognomonic indications of rheumatic fever. The cause in these cases must, therefore, remain unknown. It is difficult to ascertain whether the curious anomaly of the mitral valve in Case 7 represented a congenital aberration or the organization of thrombi formed at the time of rupture of the chordae tendineae.

There was no difference in frequency of rupture of the chordae tendineae to either of the cusps in this series. In three cases (Cases 2, 3, and 5), the ruptured chordae tendineae were attached to the anterior cusp; in three (Cases 1, 6, and 7), to the posterior cusp; and in Case 4, one chorda tendinea of each cusp was ruptured. The point of rupture was nearer the papillary muscle than the free margin of the valve. In fact, the free ends attached to the valve were easily seen when the heart was opened, and were several millimeters in length, whereas prolonged search usually had to be made for the small nodules representing the ends attached to the papillary muscles. The number of ruptured chordae tendineae varied from one (Case 6) to very many (Case 3). In all instances except Case 6, more than one chorda tendinea was ruptured.

It has often been suggested that accidental cutting of chordae tendineae in opening the heart at necropsy has been confused with ante-mortem rupture by the pathologist. Especial care was taken in each of these cases to avoid this error. The ballooning of the cusp to which the ruptured chordae tendineae were attached was noted, and, in several instances, the free ends of the chordae tendineae were seen in the valve orifice before the ventricles were opened (Fig. 1). Furthermore, the bulbous enlargements of the ends of the ruptured chordae tendineae attached to the valves and the character of the portions on the papillary muscles leave no doubt as to the ante-mortem nature of the process. This was also verified by histologic examination in four cases; in the other three the hearts were preserved as gross specimens without microscopic study.

The stumps of the ruptured chordae tendineae were composed of mats of hyalinized and partially degenerated connective tissue, with a cover-

ing of endothelium (Figs. 2 and 6). The process of scarring extended for some distance into the subjacent myocardium, and calcification was occasionally found there. In Case 3 we regard the gross and microscopic appearances as indicating that chordae tendineae ruptured at two periods, separated by a long interval. This provided material for study of the tissue sequences consequent to rupture. At the time of rupture, thrombi form over the severed ends and there may be small hemorrhages in the surrounding tissues. As these become organized, the surfaces exposed to the blood stream are endothelialized. The calcification may have taken place in degenerated connective tissue, but it is also possible that it may have been deposited in areas of hemorrhage.

The papillary muscles to which the ruptured chordae tendineae had formerly been attached were atrophied in some instances and hypertrophied in others. If all the chordae tendineae attached to one of the cusps were ruptured (as in Case 3), the corresponding papillary muscle underwent atrophy. Under these circumstances there could be no tension on the papillary muscle at any period of the cardiac cycle, and the muscular tissue therefore became atrophied through disuse. On the other hand, the rupture of one or a few chordae tendineae led to hypertrophy of the papillary muscle if the rest of the chordae tendineae attached to that structure remained intact, because of the increased work imposed by the mitral regurgitation (Cases 4, 5, and 7). A confirmation of this interpretation was found in Case 2. Eight chordae tendineae attached to one portion of the anterior cusp were ruptured, but the rest of the chordae tendineae of this cusp were intact. The portion of the papillary muscle to which the 8 ruptured chordae tendineae had been attached had undergone atrophy, whereas the part with intact chordae tendineae showed very marked hypertrophy (Fig. 3). The fact that there were striking changes in the papillary muscle is a further indication that the rupture had taken place a considerable time before death.

The weight of the heart was increased in all patients. It varied from 420 grams to 860 grams, with an average of 580 grams. Since there were other severe cardiac lesions in some of the cases, this hypertrophy cannot be attributed to rupture of the chordae tendineae entirely. However, in the case of the patient with the largest heart (Case 3), the lesions other than rupture of chordae tendineae were minor. It appears, therefore, that rupture of chordae tendineae of the mitral valve, with the consequent mitral regurgitation, leads uniformly to a considerable degree of cardiac hypertrophy regardless of what other lesions may be present.

In all cases in this series, the heart as a whole was dilated. The relative degree of dilatation of the chambers varied from patient to patient. It is worth noting, in passing, that in Cases 5 and 6, there was rather marked dilatation of the tricuspid valve, and that the measurements of the tricuspid valve were at the upper limits of normal in the other cases.

In view of the pathologic changes which have just been discussed, it is possible to re-evaluate the relation of chest trauma and of violent exertion to rupture of the mitral chordae tendineae. It is clear that chordae which are on the verge of rupture might well break under such circumstances, just as, presumably, normal chordae break as the result of severe external violence. However, most of the patients in this series gave no such history. It therefore appears that exertion and trauma are not of primary causative importance in the rupture of diseased mitral chordae tendineae, but may occasionally determine the moment at which the break occurs.

The symptoms which appear after rupture of the mitral chordae are not specific for this condition. They are those of congestive heart failure, which may be abrupt or insidious in onset and progressive or remittent in its course. The history, however, is of the first importance if it can furnish satisfactory evidence that the typical murmur made a sudden appearance. This will usually consist of a reliable statement by a previous examiner that no murmurs were present at some time in the months or years immediately preceding the development of symptoms.

All seven patients had a loud, usually harsh or coarse, precordial systolic murmur, maximal in the region of the apex and left sternal border. In six cases this was accompanied by a thrill, also maximal in that area, or palpable only there. Three patients showed some variation in the intensity of the murmur, including the two who were under observation for the longest period. In these two the thrill was not present at all times. Two patients also had low-pitched apical diastolic murmurs. In one instance, Case 4, in which the murmur was accompanied by a diastolic thrill, there was a well-marked, firm thickening of the mitral cusps which might have accounted for the diastolic murmur. In the other, Case 2, the murmur was faint and irregularly heard. Here the cusps were moderately thickened, but there was no stenosis. The degree of fibrosis of the valve was approximately the same as in Cases 1, 3, 6, and 7, in which no diastolic murmurs could be heard. However, in Case 2, there was the unusually large number of eight ruptured chordae attached to the anterior cusp. It is possible that freely movable chordae on the valve cusps may, in some instances, contribute to the production of a diastolic murmur. Diastolic murmurs have been reported in four cases of rupture of a papillary muscle without disease of the mitral valve itself.[3-6] In two instances of rupture of a papillary muscle[7, 8] in which adequate observations appear to have been made, no murmur was heard. It is conceivable that rupture of chordae tendineae might also fail to produce a murmur.

The heart was examined roentgenologically in four cases. In Cases 1 and 2, in neither of which was there a significant mitral stenosis at autopsy, moderate dilatation of the left atrium was observed roentgenologically. The left atrium in Case 1 exhibited a systolic pulsa-

tion. Dr. M. C. Sosman, in a personal communication, has noted this in two other patients who are still living. He feels that the sign is strongly suggestive of rupture of the mitral chordae tendineae. If further study confirms this, the observation will be of great assistance in the diagnosis of the condition. It is actually a sign of very brisk mitral regurgitation.

Electrocardiograms were taken in all instances. Five patients, including two with hypertension, presented left axis deviation. Three patients had auricular fibrillation, which in one instance developed during the hospital course.

An estimate of the interval between rupture of the chordae and the onset of clinically evident congestive heart failure is extremely difficult, but the evidence suggests that this interval may last a number of months and possibly even years. In the only instance (Case 1) in which rupture of the chordae could be dated definitely by the appearance of a murmur, nine months elapsed before the patient experienced outspoken symptoms of congestive failure, in spite of marked hypertension for at least the preceding ten years. In Case 6 the patient had been told he had a heart murmur eight years before his death, and for two years had had some dyspnea on exertion. In Case 7, the patient had a loud precordial systolic murmur six years before his final admission to the hospital. However, an anomalous insertion of chordae on the valve, rather than rupture of the chordae, may have accounted for the murmur during part of this time. In Case 2, the patient had had exertional dyspnea for three years before his hospital admission, and the autopsy observations indicated that rupture of the chordae tendineae had antedated by some time the appearance of definite and progressive congestive failure. It is, however, doubtful that it took place as long as sixteen years before, during his struggle in quicksand. The post-mortem examination in Case 3 showed that chordae had ruptured on at least two separate occasions, one shortly before death. The patient was known to have had a loud murmur at least six months before death, at a time when he was having only relatively mild symptoms. There is no satisfactory evidence to date the time of rupture in Cases 4 and 5. In no instance was it clear that rupture of the chordae produced any significant immediate symptoms. This was also the experience of Frew,[1] who reported rupture of the chordae in a child of eight years, and of von Albertini,[9] who described the case of a 63-year-old man whose rupture was evidently the result of violent chest trauma. Frothingham and Hass[2] dated the accident in their case from an attack of paroxysmal nocturnal dyspnea which was followed by progressive congestive failure lasting until death, eight months after the attack. It is, however, not at all uncommon for patients with long-standing valvular disease to develop sudden congestive failure from which they never recover.

The diagnosis of rupture of the chordae tendineae of the mitral valve should be entertained particularly in the case of a middle-aged or elderly person who has suddenly developed, without dramatic incident, a loud precordial systolic murmur, maximal at the apex and left sternal border, where it is usually accompanied by a thrill. An apical diastolic murmur may also be present. Congestive failure is not likely to make its appearance for months or even years after the onset of the murmur. Auricular fibrillation sometimes occurs. Roentgenograms may show enlargement, and even a systolic pulsation, of the left atrium.

The differential diagnosis includes bacterial endocarditis, rupture of other valves, rupture of a papillary muscle, and spontaneous perforation of an infarcted interventricular septum.

Bizarre murmurs sometimes occur during the course of bacterial endocarditis. As already stated, chordae may be ruptured as the result of an ulcerative process. The demonstration of organisms in the blood stream is, of course, usually possible.

Any valve may be ruptured by severe external violence.[10, 11] Spontaneous rupture or retroversion of a syphilitic aortic valve cusp may produce loud diastolic murmurs and thrills.[12] The location and character of the murmur, the evidences of free aortic regurgitation, and positive serologic reactions should easily differentiate this condition.

Quite a different course usually attends the spontaneous rupture of a papillary muscle from that which follows rupture of the mitral chordae tendineae. Rupture of a papillary muscle is likely to precipitate an immediate cardiac catastrophe. Twenty-five instances of this accident have been described in all, but only the seventeen reported since 1909 are suitable for analysis. Of these patients,[3, 4, 7, 13-18] ten apparently died within twenty-four hours and six[5, 16, 19-22] within fifteen days. One lived for ten months.[6] Rupture of the muscle is usually marked by acute pulmonary edema and peripheral circulatory collapse, even syncope. This results from the circumstances under which the accident occurs. Spontaneous rupture of a papillary muscle is almost always occasioned by an acute myocardial infarct which has involved the particular muscle. The myocardial reserve is therefore slight, and the free mitral regurgitation caused by papillary rupture is an additional cardiac burden which is usually sufficient to produce severe and rapid heart failure.

Both rupture of a papillary muscle and perforation of the interventricular septum may give rise to cardiac signs similar to those produced by rupture of the chordae tendineae. There has been great variation in the murmurs reported in instances of rupture of a papillary muscle. In twelve reported cases in which an examination of the heart was recorded, there have been four instances with systolic murmurs,[16, 20-22] usually loud and maximal at the apex; one

with an apical diastolic murmur;[8] three with systolic and diastolic murmurs;[3, 5, 6] two in which no murmur could be heard;[7, 8] and two in which a murmur was heard, but not timed.[4, 18] Sager[23] has described the signs of perforation of the interventricular septum as a precordial systolic murmur and thrill, usually maximal over the fourth and fifth intercostal spaces along the left sternal border, or over the lower part of the sternum. Later observers have been in agreement with this. Both accidents are almost always preceded by acute myocardial infarction. The history and clinical and laboratory observations which are characteristic of infarction should in most instances serve to differentiate these conditions from that produced by rupture of the chordae tendineae.

Rupture of the mitral chordae tendineae thus occurs occasionally in the absence of bacterial endocarditis. The condition can be diagnosed during life with a fair degree of accuracy. Since there is a certain similarity in the progress of the disease, a correct diagnosis should make possible a more accurate prognosis.

SUMMARY

The histories and pathologic observations in seven cases of rupture of the mitral chordae tendineae are reviewed. Patients with bacterial endocarditis were excluded from the series. All showed fibrosis and chronic injury of the mitral valve. In two, the lesions were those of rheumatic heart disease; in the remainder, the changes suggested quiescent rheumatic disease, but were not pathognomonic.

The chordae of the two valve cusps were ruptured with equal frequency in this series, and usually more than one was broken. The point of rupture lay close to the papillary muscle. The stumps consisted of hyalinized and partially degenerated connective tissue, with a covering of endothelium. Scarring extended into the subjacent myocardium. The corresponding papillary muscles underwent atrophy if all their chordae were broken, but showed hypertrophy if a number were left attached. It was clear from inspection that rupture of the chordae must have allowed a high degree of mitral regurgitation. All hearts were dilated and hypertrophied, with an average weight of 580 grams. The histories of the patients did not indicate that external violence or vigorous exertion were etiologic factors of primary importance in rupture of the mitral chordae tendineae.

The symptoms after rupture of the mitral chordae tendineae are those of congestive heart failure, which may be insidious or abrupt in its onset and progressive or remittent in its course. Months or even years may elapse between rupture and the onset of frank congestive failure.

Rupture of the chordae is suggested by the sudden appearance of a loud precordial systolic murmur, maximal at the apex and left sternal border, where it is usually accompanied by a thrill. An apical

diastolic murmur may also be present. Auricular fibrillation sometimes occurs. Roentgenograms show cardiac enlargement, and fluoroscopic examination may demonstrate systolic pulsation of the left atrium.

The differential diagnosis includes bacterial endocarditis, rupture of a valve cusp, rupture of a papillary muscle, and perforation of an infarcted interventricular septum.

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THE EFFECT ON THE BLOOD PRESSURE OF NORMAL PERSONS AND HYPERTENSIVE PATIENTS OF GLYCERYL TRINITRATE, SODIUM NITRITE, ERYTHROL TETRANITRATE, AND MANNITOL HEXANITRATE

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OUR knowledge of the relative action on blood pressure of nitroglycerin, sodium nitrite, erythrol tetranitrate, and mannitol hexanitrate* is taken largely from reports which appeared prior to 1913.[1-6] At present these drugs are widely used, and their efficacy and applicability deserve further study. In the experiments reported herewith, the four most commonly used "nitrite" drugs were administered in rotation to a number of patients, and the blood pressure effects observed. The results, in general, confirm the observations of the earlier workers.

METHOD

Normal persons and hypertensive patients in the Strong Memorial Hospital and Rochester Municipal Hospital (see Table I for details concerning the patients) were given the four drugs in rotation. The patients were led to believe that the blood pressure measurements were a part of their routine management. They were not removed from the divisions for the tests, and carried on slightly restricted but essentially normal activities.

The blood pressure of each subject was recorded at intervals of one minute during the control period of thirty minutes or less. Then a drug was given, and measurements were made at one-minute or two-minute intervals until the drug action was complete and the blood pressure had

TABLE I

DATA ON PATIENTS

		NORMAL	HYPERTENSIVE
Number		19	19
Sex:	Males	10	12
	Females	9	7
Age:	Range	15-81	20-74
	Average	35	51
Predrug pressure:			
	Systolic	118±11	184±25
	Diastolic	75±8	104±18

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*Because of the chemical instability of mannitol hexanitrate, this compound was used in the form of Maxitate, a stabilized preparation furnished by the R. J. Strasenburgh Company, which contains lactose and starch as diluents.

become normal. Rest periods were permitted for the longer acting drugs. Examples of the records are shown in Fig. 1; the upper record is of a hypertensive patient, and the lower record is of a normal subject. Three observers made the blood pressure readings; each one used

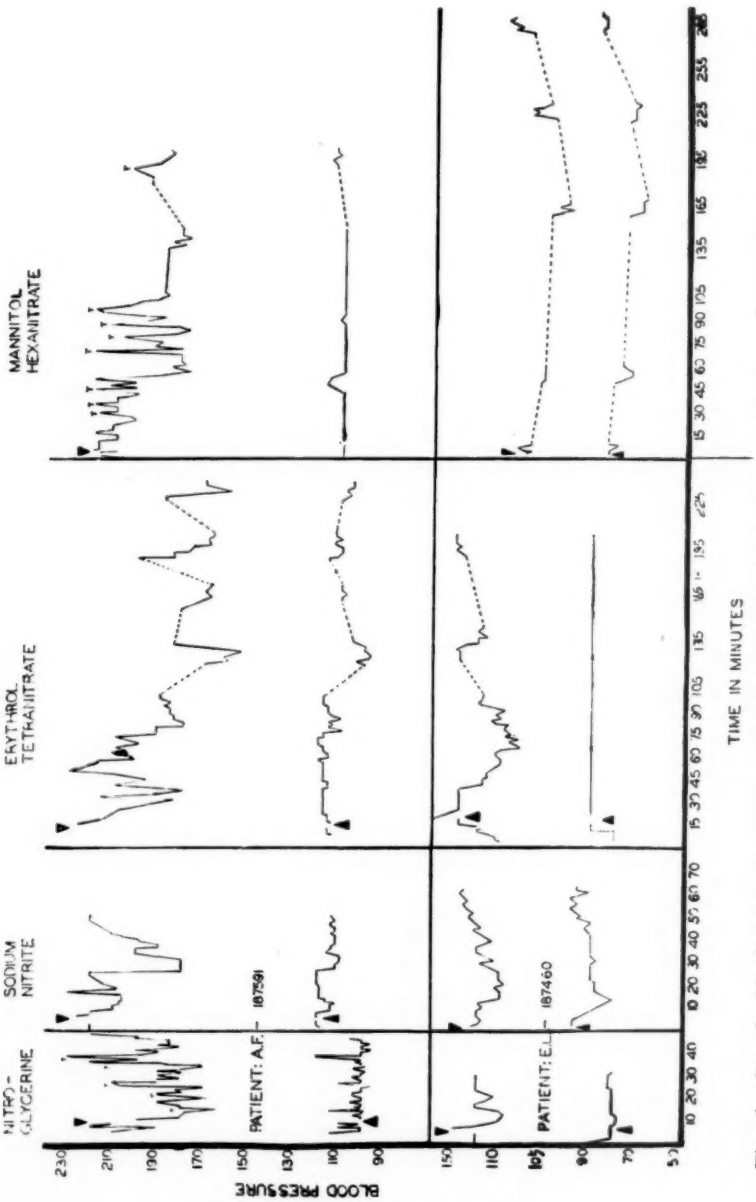

Fig. 1.—Sample blood pressure records. These charts illustrate the general plan of the experiment. Each of four drugs was given to the same patient (compare Tables III and IV). The records of two patients are shown: that of A. F., a hypertensive patient, shown above, shows marked emotional lability; talking (T) produced sharp momentary increases in systolic blood pressure; that of E. L., a normal person, shown below, gives a fairly good comparison of the amount and duration of decrease in blood pressure for each of the four drugs.

the method to which he was accustomed. All measurements were made on the same arm. A lowering of blood pressure was ascribed to the drug only when the pressure fell below the lowest readings in the control period.

The doses of the four drugs and the routes of administration were as follows: nitroglycerin, 0.006 Gm. sublingually and orally; sodium nitrite, 0.13 Gm. (sometimes 0.065 Gm.) orally; erythrol tetranitrate, 0.016 Gm. orally; and mannitol hexanitrate, 0.032 Gm. orally.

Amount of Fall in Blood Pressure.—Of the subjects who showed a well-sustained fall of blood pressure, not many had a very large decrease. Fig. 2 pictures the lowering of systolic pressure produced by each of the drugs. Each solid bar represents the average fall in systolic blood pressure following the drug specified. There was almost never a gradual decline or return of the blood pressure. Occasionally, there were isolated values 10 to 20 mm. lower than the general level of blood pressure during the period of drug effect. Such isolated occurrences should not be taken as an index of drug action. If relief of hypertension is to be of value, it should be sustained for sufficient time to relieve the myocardium of its burden. Therefore, average blood pressure for the period of drug effect was recorded throughout.

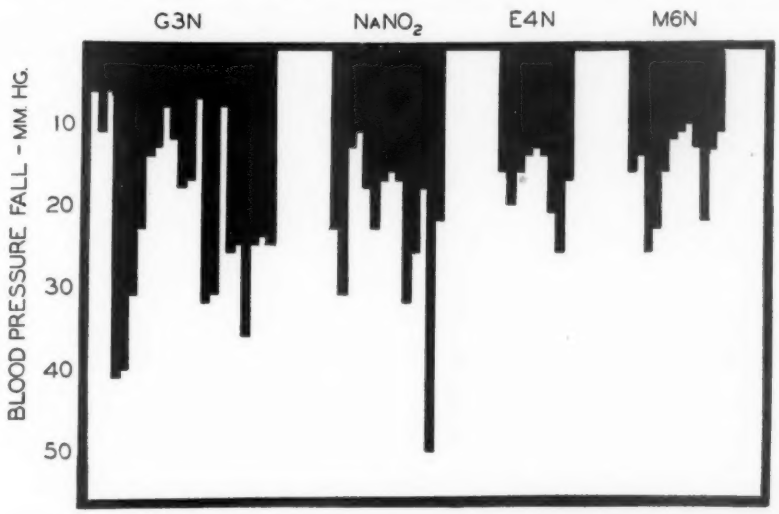

Fig. 2.—Fall in blood pressure produced by the four drugs. G3N = glyceryl trinitrate; $NaNO_2$ = sodium nitrite; E4N = erythrol tetranitrate; M6N = mannitol hexanitrate. Each solid bar represents the fall in blood pressure after the drug specified. Note that the average blood pressure lowering is of the same order for each drug.

From Fig. 2 it is seen that the greatest individual variation in the amount of blood pressure lowering occurred with nitroglycerin and sodium nitrite. Also, in isolated cases, the greatest actual amount of fall followed these two drugs. With erythrol tetranitrate and mannitol hexanitrate there was never a marked fall, but most of the subjects who responded gave fairly consistent responses. With each of the drugs the average fall in blood pressure was about the same (Table II); the statistical analysis of the data is given in the footnote to Table II. In

TABLE II

MEAN EFFECTS OF DRUGS ON BLOOD PRESSURE

	NORMAL				HYPERTENSIVE			
	$NaNO_2$	G3N	E4N	M6N	$NaNO_2$	G3N	E4N	M6N
Maximum drug effect (mm. Hg)	$-\frac{10}{2}(13)$	$-\frac{11}{1}(14)$	$-\frac{7}{2}(12)$	$-\frac{7}{2}(12)$	$-\frac{16}{4}(17)$	$-\frac{21}{1}(17)$	$-\frac{14}{5}(12)$	$-\frac{12}{4}(16)$
Drug effect commences (min.)	7	2	36	72	7	3	34	42
Drug effect ends (min.)	79	18	247	329	61	26	335	291

The standard deviations of each average blood pressure fall are as follows:

		$NaNO_2$	G3N	E4N	M6N
"S"	Systolic	10	8	7	9
	Diastolic	5	5	6	8

Parenthetical figures indicate the numbers of experiments yielding the figures averaged to obtain those given here.

G3N = glyceryl trinitrate.

E4N = erythrol tetranitrate.

M6N = mannitol hexanitrate.

The averages given above are to be compared with the "S" values: for example, the average blood pressure fall for G3N ± its standard deviation is 11±8. "S" values are calculated according to Fisher.[7]

general, a patient who responds to one of these drugs will have an average fall in blood pressure of 10 to 20 mm. of mercury.

Time Required for Drug to Take Effect.—The average times before the onset of a fall in blood pressure after the administration of the drugs are shown in Table II. The time of onset is fairly constant for nitroglycerin and sodium nitrite, but varies widely for erythrol tetranitrate and mannitol hexanitrate. This variation may be ascribed to the slow absorption of the latter two drugs.

Duration of Blood Pressure Responses.—Table II also gives the average duration of the period of blood pressure decrease after each of the drugs. The duration of fall after nitroglycerin was surprisingly constant. For the other three drugs the durations varied widely. In order of duration of effect, nitroglycerin $<$ sodium nitrite $<$ mannitol hexanitrate $=$ erythrol tetranitrate. However, this is an inadequate statement; the nitroglycerin effect was limited to about fifteen minutes, the sodium nitrite effect lasted about an hour, and erythrol tetranitrate and mannitol hexanitrate maintained an effect for about four hours on the average (see Tables III and IV).

Blood Pressure Stability and Lability.—The minute-by-minute fluctuation of blood pressure was surprising. Often, without apparent cause, the blood pressure of some subjects (normals as well as hypertensives) would vary 10 to 20 mm. Hg and return to its previous level, all in the space of two readings at one-minute intervals. No apparent change in the subject would be seen, nor would the pulse rate change. In other instances the pressure would remain constant within 5 mm. throughout the period. In some cases a considerable elevation occurred while the subject was talking or laughing. No relation between this type of phenomenon and response to a drug could be ascertained. One patient with quite a labile blood pressure is worthy of note. She (A. F., Fig. 1) had readings taken at one-minute intervals that fluctuated between 165/98 and 230/120, depending on whether she was quiet or talking and laughing. Her pulse rate varied between 76 and 92 per minute without concomitant changes in blood pressure.

Pulse Pressure.—Many subjects had a lowering of systolic pressure without any change in the diastolic; however, not a single subject had a fall of diastolic pressure as great as that of the systolic. When these drugs produced a fall of blood pressure, the effect was nearly always to reduce the pulse pressure.

Pulse Rate.—The pulse rate was counted between every three or four blood pressure readings. There was seldom any increase in pulse rate accompanying a fall of systolic pressure or decrease in pulse pressure.

Response to Drug.—Fig. 3 shows the number of subjects studied and the percentage who showed a blood pressure response to each of the

TABLE III

DATA ON NORMAL PERSONS

PATIENT	AGE (YR.)	EFFECT OF DRUG ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE								DURATION OF DRUG EFFECT							
		G3N		$NaNO_2$		E4N		M6N		BEGINNING				END			
		P	ΔP_{max}	P	ΔP_{max}	P	ΔP_{max}	P	ΔP_{max}	G3N	$NaNO_2$	E4N	M6N	G3N	$NaNO_2$	E4N	M6N
BR	17	132/80	−16/0	126/81	−14/−4	126/83	−6/−6	124/80	−12/−3	2	5	63	38	22	19	523	489
DO	15	107/76	−8/−2	103/70	+4/+2	112/64	−8/−6	112/75	−18/−16	2	7	39	40	16	21	445	475
LA	65	140/83	−14/−2	151/98	−20/−16	143/84	−8/0	121/82	−18/−12	2	4	56	46	17	54	92	252
CI	16	107/68	−4/0	104/67	0/0	112/67	0/0	104/68	−2/−2	4			60	7			306
GR	38	118/70	−6/+10	111/74	−2/+2	121/77	−6/+6	120/74	−8/+4	6	12	50	128	17	30	246	304
GA	23	120/73	−12/0	121/68	−20/−2	121/61	−14/+8	118/61	−22/−8	1	9	27	22	13	344	370	306
FO	56	112/77	−10/−2	112/73	−10/+4	120/90	0/0	114/80	0/0	2	5			14	29		
AS	81	118/75	−28/−10	119/69	−28/−8	114/74	−18/−10	105/67	0/0	2	7	16		23	191	197	
PA	16	119/81	−18/−4	119/86	0/+2?	110/81	+4/+4	113/82	+2/0	1		34	95	31		298	321
CO	32	123/78	0/+2?	129/80	−12/0	123/81	−16/−10	124/75	−10/0		12	32	134		46	240	310
SP	40	117/83	0/−2	126/93	−6/−4					2	4			17	21		
MN	18					97/63	−12/−6	105/64	0/−16			3	87			20	197
PU	40	108/70	−14/−8							2				15			
AR	31	106/66	−10/0							1				22			
GO	24	115/68	−7/0							2				14			
MC	70			141/69	−18/−0										27		
ER	20			116/75	0/0												
WE	29					119/61	0/0										
HO	42							108/64	0/0								

P = blood pressure in mm. of Hg, systolic/diastolic.

ΔP_{max} = maximum changes of pressures systolic/diastolic.

TABLE IV

DATA ON HYPERTENSIVE PATIENTS

PATIENT	AGE (YR.)	EFFECT OF DRUG ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE								DURATION OF DRUG EFFECT							
		G3N		$NaNO_2$		E4N		M6N		BEGINNING				END			
		P	ΔP_{max}	P	ΔP_{max}	P	ΔP_{max}	P	ΔP_{max}	G3N	$NaNO_2$	E4N	M6N	G3N	$NaNO_2$	E4N	M6N
MA	42	144/98	0/0	167/98	−14/0	156/98	0/0	146/99	0/0		8				35		
FA	55	205/106	−24/0	220/119	−40/−8	220/116	−68/−28	213/110	−30/0	2	3	44	38	34	40	674	267
HU	61	179/90	+12/+12	168/95	−20/−10	186/94	−14/0	177/89	0/+12	5	3	22	25	25	44	164	60
WH	61	163/87	−14/0	168/91	0/0	175/82	−20/−14	167/88	0/0	1		13		20		361	
CN	64	206/110	−18/+6	209/119	0/0	188/94	0/−14	199/102	−10/−8	7		13	18	31		141	418
FD	20	184/103	−10/0	171/95	−22/0	160/101	0/0	160/94	0/+14	3	31		88	24	27		370
FD				156/102						5					38		
DA	49	155/97	−20/0	174/106	−30/−8	171/109	−20/−14	151/109	0/−8	1	4	42	24	27	93	276	61
CK	42	169/113	−18/+4	182/117	−20/−6	160/105	+4/+14	163/101	−10/+8	1	6	99	42	19	82	478	478
AD	56	201/110	−60/−6	194/107	−24/−10	152/90	−20/−10	167/91	0/0	2	8	9		31	68	134	
RA	68	183/100	+10/+10	181/88	−8/0	170/88	+28/+8	182/89	−28/−18	12	5	9	34	23	39	154	214
TA	56			197/134	−42/−22						9				243		
TA		161/103	−12/−8	163/111	−12/−8	169/125	−34/−26	163/113	−20/−12	2	8	46	104	37	32	750	830
DU	73	208/101	0/0	200/94	+5/0	183/89	−20/−4				3	41			9	221	
DU		205/102	−20/0	199/94	−27/0					2	6			15	69		
LE	65	169/78	−68/−10	179/73	−18/+2			197/100	−20/−10	1	5		20	44	35		73
SE	48	252/147	−29/−14					251/139	−52/−22	2			30	17			307
FR	74	225/107	−40/0					203/105	0/0	1				19			
FR		210/110	−52/−10							1				21			
CA	47			210/165	0/0												
PO	58							207/106	0/0								
WN	31							227/171	−14/−14				37				119

drugs. With each drug a greater percentage of hypertensive patients exhibited a fall in blood pressure (except for erythrol tetranitrate) than of normal persons.

Untoward Reactions.—Of 32 subjects who received single doses of nitroglycerin, 8 had pounding headache, 1 had a hot feeling in the head, and 1 had dizziness. Of 28 subjects who received sodium nitrite, 1 had occipital pounding and 1 had nausea followed by vomiting. Of 24 who received erythrol tetranitrate, 4 had pounding headache. Of 28 who received mannitol hexanitrate, none had side effects. The untoward reactions were about evenly divided between normal and hypertensive subjects.

Of 15 patients who were given daily doses of mannitol hexanitrate in the clinic, 6 experienced such severe side effects that they were unable to continue taking the drug. Two others had effects that were mild and quickly disappeared during continuation of the regimes. The undesirable drug effects were: full feeling in the head, dizziness or headache, gastric discomfort without nausea or vomiting, abdominal cramp with nausea, mild diarrhea, and palpitation. Headache occurred in 4 cases, gastrointestinal symptoms in 4, palpitation in 2, and dizziness in one.

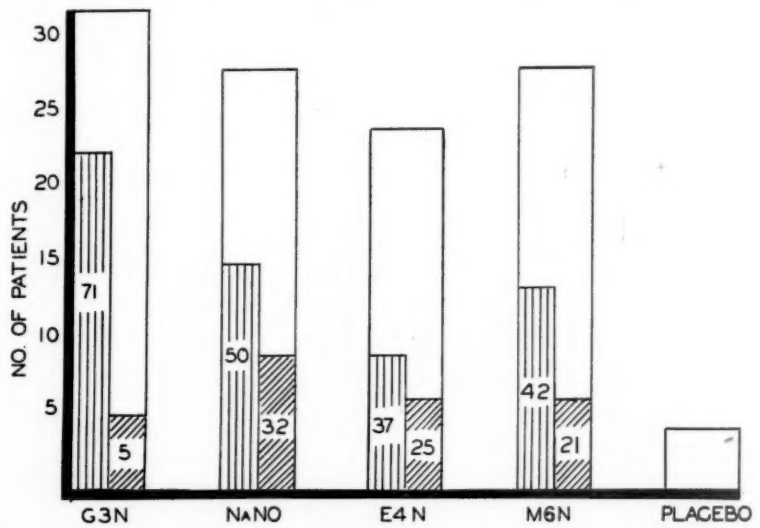

Fig. 3.—Number of subjects with each drug and percentage who showed a fall in blood pressure. The height of the open columns is the number of patients; the heights of the hatched areas give the number of patients in which a fall in systolic pressure (vertical hatch) and diastolic pressure (slant hatch) was observed, respectively. The numbers in the hatched areas represent the percentages of the patients who responded with lowered systolic and diastolic pressures, respectively.

DISCUSSION

Reliability.—For a given patient, the results with any one of these drugs are unpredictable. Some patients have no response, some have a lowering for only a short period of time, some have such a small fall in pressure that the drug seemingly will be worthless as an agent for

diminishing hypertension. There are a few ideal subjects. These have a good response that is sustained at a markedly lower level for a fairly long period. If a patient responds to one of these drugs, it does not mean that he will respond to any or all of the others. The only way in which the value of one of these drugs for a given patient can be judged is for that patient to take the drug, with several measurements of blood pressure after the administration of the drug at appropriate intervals.

The results with nitroglycerin were most reliable. We feel that this is because of its more rapid action, which is probably due to quicker and more constant absorption. Sodium nitrite was intermediate. Erythrol tetranitrate and mannitol hexanitrate were about equal; mannitol hexanitrate seemed to start its action a little later than erythrol tetranitrate, but the duration of maintained lowering was about the same for both. However, after mannitol hexanitrate, a larger percentage of subjects had a fall in blood pressure and there were fewer disagreeable side effects.

Symptomatic Relief.—In a group of 8 hypertensives who were followed for several months during treatment in the clinic with mannitol hexanitrate a fall in blood pressure could not be demonstrated. The important observation in this group was the relief of symptoms. This was often striking. In a control group of 11 patients, such definite symptomatic relief was not seen. Although the series is small, we feel that there is sufficient evidence to indicate the trial of this drug for long-standing hypertensives. If it relieves their symptoms, it is a worth-while therapeutic adjunct.[8, 9]

SUMMARY

1. Nitroglycerin, sodium nitrite, erythrol tetranitrate, mannitol hexanitrate, and a placebo were given to normal and hypertensive subjects, and blood pressure measurements were made at brief intervals until the effect of the drug was over. Each of the thirty-eight subjects received one or more of these substances, and most received all four "nitrite" drugs.

2. Of the subjects who were given these drugs, 51 per cent had a fall of systolic pressure, and 23 per cent had a lowering of diastolic pressure. The systolic fall was almost always greater than the diastolic. None had a fall in blood pressure after the administration of a placebo.

3. The amount of the fall in blood pressure in hypertensive patients varied greatly, but the averages were as follows: nitroglycerin, 16/4 mm. Hg, sodium nitrite, 21/1 mm., erythrol tetranitrate, 14/5 mm., and mannitol hexanitrate, 12/4 mm. In normal subjects, the average fall in blood pressure was as much as 10 mm. less than the corresponding figure for hypertensives.

4. The period between the administration of the drug and the beginning of the fall in blood pressure was variable. For nitroglycerin this

interval averaged 2 minutes; for sodium nitrite, 7 minutes; for erythrol tetranitrate, 35 minutes; and for mannitol hexanitrate, 55 minutes after the drug was given.

5. The average duration of blood pressure lowering was as follows: nitroglycerin, 20 minutes; sodium nitrite, 62 minutes; erythrol tetranitrate and mannitol hexanitrate, about the same, 256 and 252 minutes, respectively. With the last two drugs there was wide variation in the duration.

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CONGESTIVE HEART FAILURE AND ELECTROCARDIOGRAPHIC ABNORMALITIES RESULTING FROM EXCESSIVE DESOXYCORTICOSTERONE ACETATE THERAPY IN THE TREATMENT OF ADDISON'S DISEASE

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THE phenomenon of fluid and salt retention resulting from the treatment of Addison's disease with desoxycorticosterone acetate has been described by many observers.[1-8] In fact, it has been noted that the patient may succumb in the course of a few days as a result of the excessive accumulation of fluid when an excess of desoxycorticosterone acetate is given. The complimentary effect of sodium and desoxycorticosterone acetate has been stressed, and the hazards of giving large doses of desoxycorticosterone acetate or desoxycorticosterone acetate and sodium chloride are therefore self evident.

In recent months, we have had two patients who developed congestive heart failure as the result of taking excessive amounts of desoxycorticosterone acetate and salt. The changes in the electrocardiograms were quite striking, and, as will be pointed out later, a good deal of information was gained from a comparison of the serial changes. Although, as stated above, numerous observers have described the hazards of giving too much desoxycorticosterone acetate in Addison's disease, the striking effect upon the electrocardiogram has not been adequately emphasized.

REPORT OF CASES

CASE 1.—A 45-year-old housewife entered the hospital Aug. 28, 1939, complaining of weakness of two years' duration. In December, 1937, her blood pressure had been found to vary from 150/104 to 160/110. She had lost 18 pounds in weight during the year before entry. Physical examination revealed a rather nervous woman with moderate, dusky-brown pigmentation of the skin of the forearms, hands, and neck. The heart was normal and the blood pressure was 90/65. On Aug. 31, 1939, the blood sodium was 141 meq./L. However, on a salt-deprivation, high-potassium test (Cutler-Power-Wilder test), the blood sodium fell to 128 meq./L. and blood chlorides to 85 meq./L. on the second day of the test. She was discharged on a high salt intake.

In May, 1940, because of irregular menses, she received a sterilization dose of x-ray to the pelvis. She returned to the hospital October 30, complaining of considerable weakness and abdominal pain lasting twenty-four hours. Her blood pressure (recumbent) was 82/60. She was given desoxycorticosterone acetate, 10 mg. intramuscularly, daily for seven days, after which she received four pellet implantations total-

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ing 508 milligrams. No extra salt was given. On Nov. 15, 1940, the blood sodium was 142 meq./L., and the potassium, 3.5 meq./L. The patient returned to the hospital March 1, 1941, complaining of weakness for six weeks; at this time her blood pressure was 90/50, and her weight was 91 pounds. Two more pellets were implanted, totaling 250 milligrams.

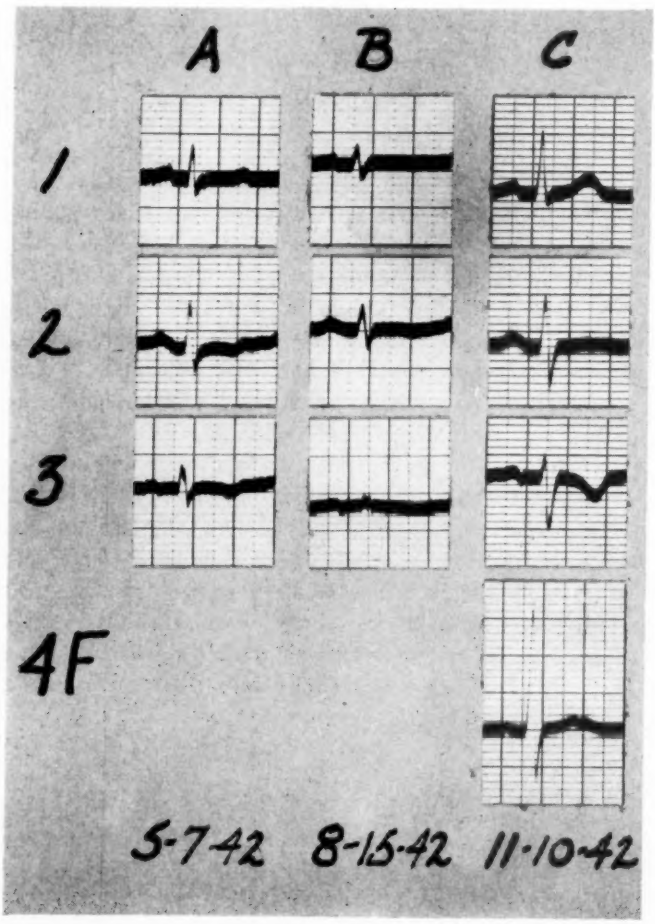
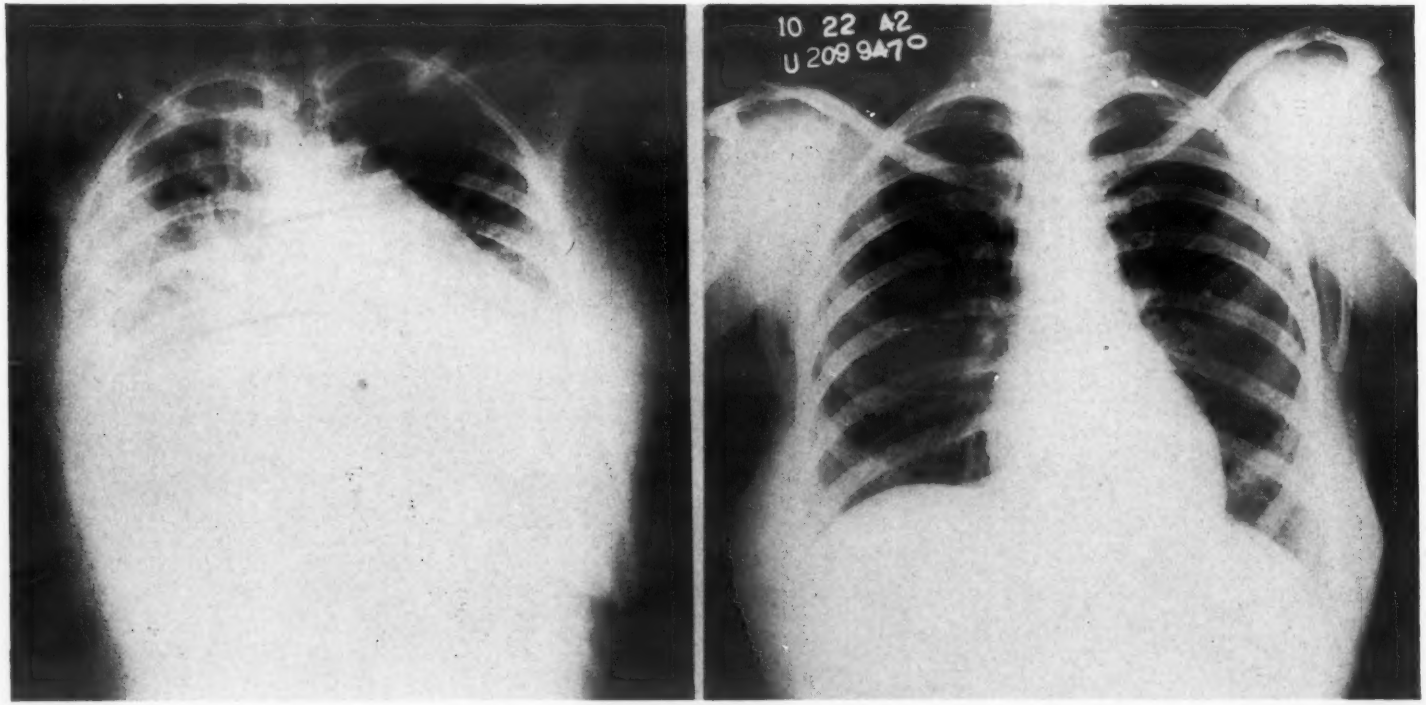


Fig. 1.—Serial Electrocardiograms in Case 1. The relatively low voltage of the QRS and T waves on May 7, 1942, suggests a slight excess of the drug. By Aug. 15, 1942, the full effect of desoxycorticosterone acetate overdosage is manifest in the electrocardiogram, with isoelectric or slightly inverted T waves in Leads I and II. After diuresis and disappearance of the congestive phenomena with adequate daily substitution of desoxycorticosterone acetate, the electrocardiogram had returned essentially to normal on Nov. 10, 1942. The patient had not had digitalis for two weeks.

The patient's health was quite good, and her strength was adequate until she returned in May, 1942, with recurrence of the weakness for a period of one month. The blood pressure was 110/75, and the blood sodium was 140 meq./L., however. The electrocardiogram at that time is shown in Fig. 1, *A*. Five pellets were then implanted, totaling 634 milligrams. On May 17, she noted some edema of the face and legs, and, on May 25, her blood pressure was 160/86, and her blood sodium,



A. *B.*

Fig. 2.—*A*, Bedside roentgenogram of the chest in Case 1, made on Aug. 24, 1942, showing cardiac enlargement and congestion of the lungs, particularly on the right. *B*, Teleoroentgenogram of the chest of the same patient on Oct. 22, 1942, revealing clear lung fields and a heart of normal size.

150 meq./L. The 3 Gm. of extra salt in her diet were discontinued. By July 22, the weight increased to 119 pounds, and her blood pressure was 126/92. The urine showed 2 plus albumin. She was readmitted to the hospital at this time because of abdominal swelling of two weeks' duration. There was some swelling of the face, shifting dullness was demonstrated in the abdomen, and the blood pressure was 128/104. No edema of the ankles was noted. Blood chemical studies revealed the following: nonprotein nitrogen, 13 mg. per cent; chloride, 111 meq., sodium, 146 meq., and potassium, 4 meq./L. A roentgenogram of the chest revealed an enlarged heart (transverse diameter, 12.9 cm., as compared to 10 cm. several months before).

On August 1, two of the five previously implanted pellets were removed. The electrocardiogram on August 15 is shown in Fig. 1, *B*. Three injections of 0.5 c.c. of mercupurin were without striking effect. On August 21, the three remaining pellets of desoxycorticosterone acetate were removed, and she was given 15 c.c. of cortical extract daily. The following day the venous pressure was 28 cm. of water, and the arm-to-skin circulation time was 21 seconds. A bedside roentgenogram of the chest was made on August 24, and is illustrated in Fig. 2, *A*. A diastolic gallop rhythm was noted at the apex of the heart. Edema over the sacrum was prominent, and the patient was orthopneic. On August 29, 1 c.c. of mercupurin was given, and the urinary output was 1,500 c.c. during the subsequent twenty-four hours. The blood pressure averaged about 130/90, and the weight remained at 118 pounds. Digitalis was then started, on September 4, in a dose of 0.13 Gm. each day, and within eight days the patient lost twenty pounds in weight, the gallop rhythm disappeared, and the heart decreased in size. The digitalis was then decreased to 0.065 Gm. every day, and the patient's condition improved rapidly. On September 25, the venous pressure was 11 cm. of water and the arm-to-skin circulation time was 19 seconds. On October 5, the electrocardiogram had shown striking improvement. The patient was discharged on October 26, at which time the digitalis was discontinued and she was receiving 1 mg. of desoxycorticosterone acetate daily, without extra salt. The weight fluctuated from 96 to 102 pounds, and the blood pressure varied from 160/120 to 120/80. The patient felt better than she had for many months. No signs of congestive heart failure or edema remained, and no digitalis was necessary. Another roentgenogram of the chest (Fig. 2, *B*) revealed remarkable improvement. On November 10, the electrocardiogram was normal. She has continued to do well, receiving daily injections of 1 mg. of desoxycorticosterone acetate. The electrocardiogram taken in July, 1943, was essentially the same as that of November, 1942.

Comment.—The clinical diagnosis of Addison's disease was clear-cut in this patient, who had been observed to have hypertension previously. In retrospect, there is little doubt that the weakness which developed in May, 1942, was not due to adrenal insufficiency. The blood sodium was normal, the blood pressure was normal, and the electrocardiogram suggested, if anything, an excessive absorption of desoxycorticosterone acetate. The subsequent course, with the appearance of definite signs of congestive heart failure after the implantation of more desoxycorticosterone acetate, was dramatic, and the low voltage of the QRS and T waves of the electrocardiogram was equally noteworthy. After the

removal of the subcutaneous pellets, the response to relatively small doses of digitalis was equally dramatic, and the electrocardiogram returned to normal. It should be noted, however, that the desoxycorticosterone acetate pellets had been removed, and that the patient might have had a spontaneous diuresis without the aid of digitalis.

CASE 2.—An 18-year-old girl entered the hospital Aug. 11, 1942, complaining of recurrent attacks of abdominal pain, with nausea, vomiting, and weakness, of twelve months' duration. In January, 1942, appendectomy was done because of one of the attacks of abdominal pain, and it was said that the patient collapsed during the operation. There had been no menses for four months before entry.

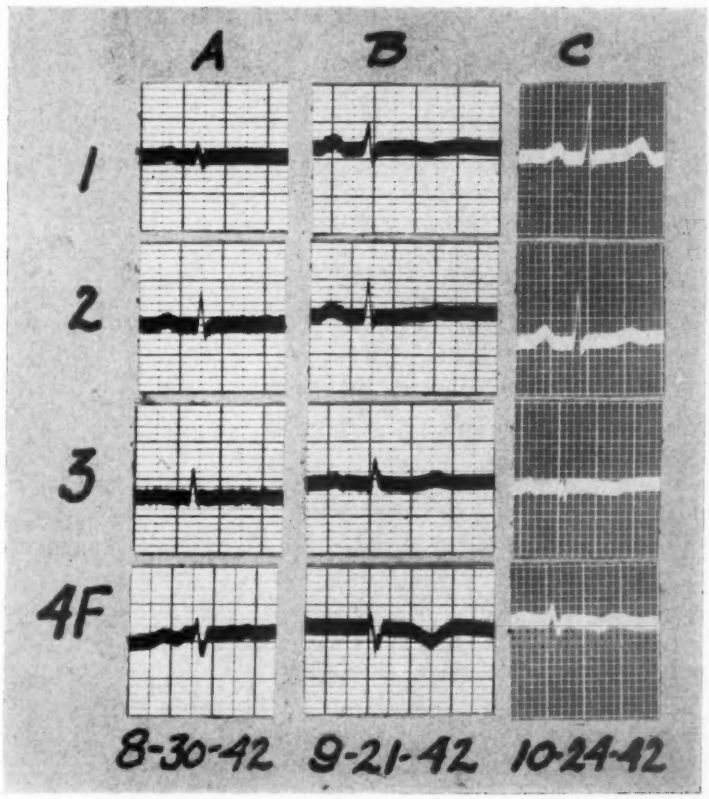


Fig. 3.—Serial Electrocardiograms in Case 2. The first electrocardiogram, Aug. 30, 1942, shows the effect of excessive doses of desoxycorticosterone acetate which was still present on Sept. 21, 1942. The T waves in Leads I and IV were inverted, and the Q-T interval had increased to 0.40 second, although the heart rate at this time was 60. The low voltage of the QRS, and very low, isoelectric, or slightly inverted T waves should be noted. By Nov. 24, 1942, the electrocardiogram had improved remarkably, as had the patient. On May 17, 1943, the T wave in Lead IV had become positive (0.5 mm.), and the limb leads were essentially the same.

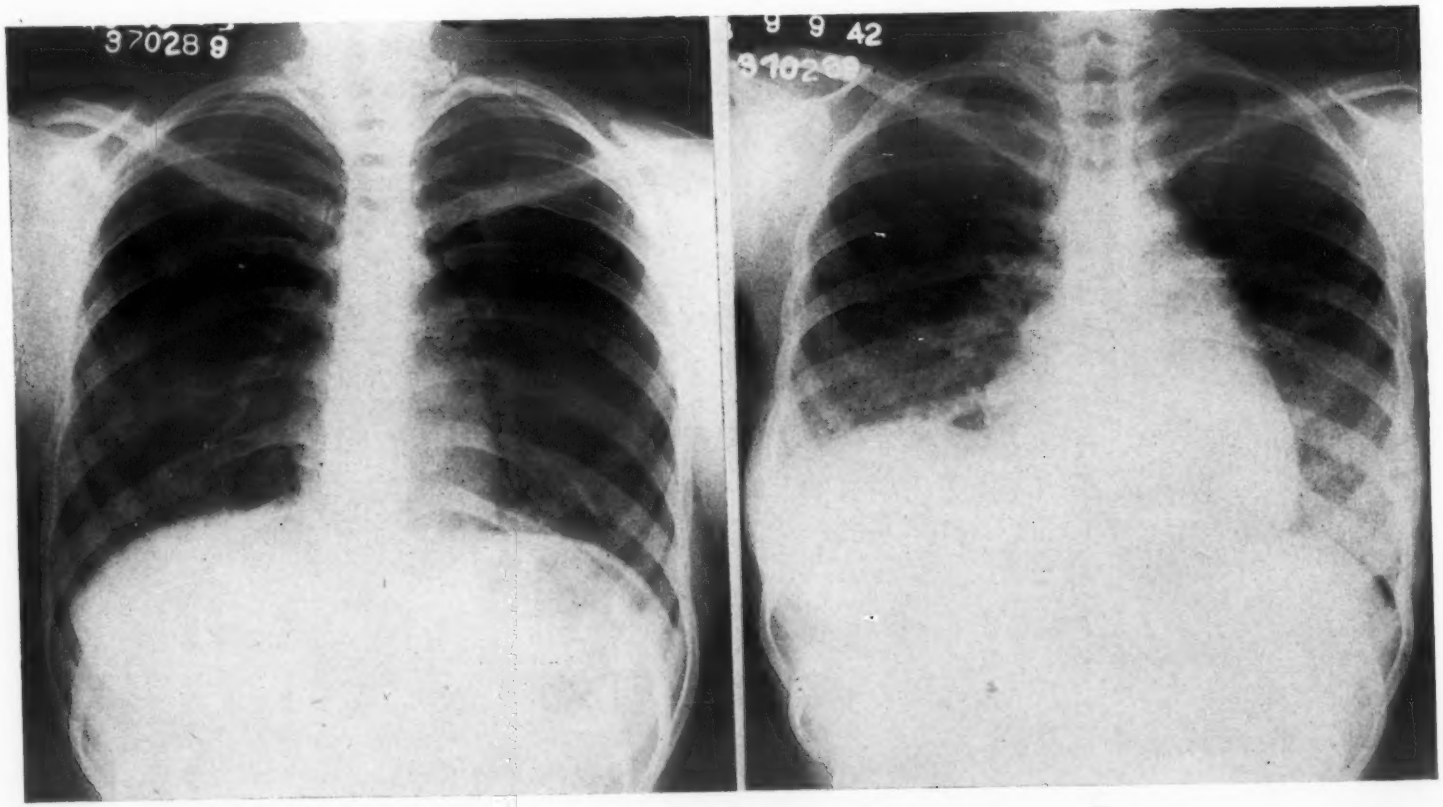
Physical examination revealed a restless, nervous girl with evidence of recent weight loss. There was characteristic pigmentation of the lips, hard palate, and abdominal scar. The heart was normal and the blood pressure was 70/40 (recumbent). Blood chemical examination revealed: sodium, 128 meq./L. sugar, 61 mg. per cent, and nonprotein nitrogen, 90

mg. per cent. On August 14, the patient received 10 c.c. of cortical extract and 20 mg. of desoxycorticosterone acetate. During the subsequent four days she received 125 c.c. of cortical extract, 105 mg. of desoxycorticosterone acetate, and 59 Gm. of salt. On August 19, some edema of the eyelids was noted, the blood pressure was 90/60, the chest roentgenogram revealed increased density of the lower lung fields which was consistent with pulmonary edema, and chemical examination of the blood revealed a chloride of 112 meq./L., a nonprotein nitrogen of 15 mg. per cent, and sugar of 145 mg. per cent. Desoxycorticosterone was then discontinued, and the patient received cortical extract in a dose of 15 c.c. daily. The signs in the chest decreased until August 28, when the patient received 7.5 mg. of desoxycorticosterone, after which she gained 5 pounds, the signs of pulmonary congestion returned, and the electrocardiogram (on August 30) was as shown in Fig. 3, *A*.

Desoxycorticosterone acetate was again discontinued, except for a mistaken dose of 20 mg. on September 2, and the patient was maintained on 15 c.c. of cortical extract without extra salt. Her condition changed little. There was some dependent edema, and, on September 9, the heart was found to be enlarged roentgenologically (an increase in the transverse diameter of 4.5 cm., i.e., from 8.9 to 13.4 cm., with poor pulsation fluoroscopically). The two roentgenograms are shown in Fig. 4. The same day the venous pressure was 15 cm. water, the intensity of the pulmonary second sound was moderately increased, and there was gallop rhythm at the apex. Digitalis, in a dose of 130 mg. daily (U.S.P. XI), was given for nine days, after which she received 65 mg. daily for five weeks. The twenty-four-hour excretion of the 17 ketosteroids on September 17 was 1.1 mg. per cent.

An electrocardiogram, taken on September 21, at which time the heart had changed little roentgenologically, although the gallop had disappeared, is shown in Fig. 3, *B*. By October 1, the transverse diameter of the heart shadow had decreased considerably (to 11 cm.), the body weight had decreased from one hundred eleven to one hundred pounds, and there was no detectable edema. The patient had her first menstrual period in six months on October 6. The dose of desoxycorticosterone acetate and cortical extract was progressively decreased, and she was discharged on October 25, taking 5 c.c. of the extract and 2 mg. of desoxycorticosterone a day.

Comment.—There was a good deal of delay in initiating the treatment of adrenal insufficiency, so that, when the diagnosis was made, unusually large amounts of desoxycorticosterone acetate were given, together with an abundance of sodium chloride. The signs of congestive heart failure were as definite as in Case 1, and the serial electrocardiograms were as remarkable. The shallow inversion of the T wave in Leads I and IV on Sept. 21, 1942, was no doubt indicative of moderate damage to the myocardium incident to the effect of excessive amounts of desoxycorticosterone acetate. The patient was receiving digitalis at the time, but in relatively small doses. Pericarditis was considered as a cause for the inversion of the T waves, but no positive evidence was ever obtained to substantiate such a diagnosis. It should be noted, likewise, that the signs of congestion developed while the blood pressure was still below normal, and without any significant tachycardia.



A. *B.*

Fig. 4.—*A*, Teleorentgenogram of the chest in Case 2, made Aug. 13, 1942, before any specific therapy. The heart is small and the lung fields are clear. *B*, Repeat teleoroentgenogram of the chest on Sept. 9, 1942, showing enlargement of the heart and moderate pulmonary congestion at the bases.

DISCUSSION

The mechanism of the heart failure in these two cases is not entirely clear. That there was an accumulation of salt and water in the body there can be little doubt, as evidenced by the increase in body weight and the development of edema. The evidence of congestive heart failure was likewise clear, namely, the increase in the size of the heart, the roentgenologic signs of pulmonary congestion, the gallop rhythm, and the rise in venous pressure. The striking rise of blood volume that occurs after the administration of desoxycorticosterone acetate to patients with Addison's disease[1] was undoubtedly an important factor in causing the congestive heart failure. This also was a factor in increasing the first patient's blood pressure to hypertensive levels.

However, a disturbance of electrolytic balance was undoubtedly of some importance in the altered physiology of the heart and the decreased efficiency of the heart muscle. It was demonstrated many years ago by Ringer[9] that potassium in proper concentration is essential for normal contraction of cardiac musculature. More recently, Follis, et al.,[10, 11] have observed morphologic changes in the cardiac muscle of rats which were maintained on a low potassium diet and forced to exercise. Similar changes were not noted in the voluntary muscles, and the changes in the cardiac muscle were not observed in control animals which received an adequate amount of potassium in the diet. Darrow and Miller[12] produced similar morphologic changes in rats and cats by daily injection of desoxycorticosterone acetate, and these, too, were prevented in control animals by the addition of potassium to the diet. It seems not unreasonable, therefore, to suppose that similar changes may have taken place in these two cases during the period when the patients were receiving excessive amounts of desoxycorticosterone acetate, which, of course, would be an important factor in the development of congestive heart failure. The serum potassium was measured in only one of these patients, and was found to be within the range of normal. This determination, however, does not indicate the status of the potassium metabolism in either the cardiac or skeletal musculature, for such stores may be depleted without appreciably affecting the serum potassium. A more accurate means of following the loss of potassium would be to ascertain the urinary excretion, which, unfortunately, was not followed in these patients. The improvement of the patients after relatively small doses of digitalis suggests that digitalis may be used to advantage in controlling or preventing the heart failure. At least, in the event of the development of congestive heart failure, digitalis should be given.

The serial changes in the electrocardiograms were quite striking, and this phenomenon, too, is undoubtedly associated with the altered electrolytic balance which occurs after prolonged treatment with desoxycorticosterone acetate, with particular regard to potassium. With the loss of cellular potassium in familial periodic paralysis,[13, 14] rather

striking alterations in the electrocardiogram have been observed, particularly loss of amplitude of the T waves. Similar but less marked changes have been observed to occur in the electrocardiogram when normal men are given desoxycorticosterone acetate for short periods of time in good-sized doses.[15]

During the treatment of patients with Addison's disease by desoxycorticosterone, the question frequently arises as to whether the patient has had too little or too much of the synthetic hormone. This is true because weakness may be the predominant symptom in either case. The weakness caused by excessive amounts of desoxycorticosterone acetate may well be associated with the loss of body potassium which results therefrom, and is to be likened to the weakness and paralysis of familial periodic paralysis. For this reason it seems wise to give small to moderate doses of potassium salts to patients suffering from excess desoxycorticosterone acetate therapy. There is usually a gain in weight after desoxycorticosterone acetate therapy, but this at times is not very striking, for some return of the weight toward normal is expected. The size of the heart is known to be an accurate index in treating Addison's disease, but comparable roentgenograms are often difficult to obtain. Serial electrocardiograms seem to be a reliable index of the status of desoxycorticosterone acetate therapy, and can be used to advantage, particularly in ascertaining whether a patient has had an excess of the synthetic hormone.

SUMMARY AND CONCLUSIONS

Congestive heart failure and electrocardiographic changes were observed in two cases of Addison's disease in which an excessive amount of desoxycorticosterone acetate was given. The cause of the decreased efficiency of the heart is discussed, and the striking alterations in the electrocardiogram (low voltage of QRS waves and flattening or inversion of the T waves) are emphasized. The changes in the electrocardiogram, particularly the T-wave changes, have been compared with the alteration of the electrocardiogram incident to a loss of body potassium. Digitalis therapy proved of considerable value in clearing up the congestion in the two cases reported here. Potassium salt by mouth may be of value in improving the efficiency of the heart muscle during desoxycorticosterone acetate toxicity.

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ADDENDUM

Since submitting this manuscript for publication three relevant reports have appeared[16-18] in the literature. The last two reports[17, 18] further emphasize the role that potassium metabolism plays in myocardial physiology during toxicity from desoxycorticosterone acetate.

AN INTERPRETATION OF AXIS DEVIATION AND VENTRICULAR HYPERTROPHY

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BRONX, N. Y.

INTRODUCTION

IN 1913, Einthoven, Fahr, and deWaart[1] developed the concept of the electrical axis and a method of measuring it in terms of the angle α.†

This concept has been of great value because it has been found that there is good clinical correlation between the recognized electrocardiographic patterns of axis deviation and conditions in which hypertrophy of the right or left ventricle exists.

Yet, as is well known, the electrical axis is not fixed, but changes from moment to moment during the inscription of the QRS complex,[2] and what is ordinarily described as the electrical axis is the reading taken at the peak of the R wave. Furthermore, in cases of right or left ventricular hypertrophy, reference to the electrical axis does not explain the RS-T deviations and T-wave changes which are often observed. In addition, there are many atypical cases of ventricular hypertrophy which do not conform to the established criteria, such as cases of left ventricular hypertrophy in which there is right axis deviation.[3] Finally, although there is a close correlation between angle α and the average direction of spread of the impulse in the auricles, no such clear correlation is found in the ventricles.

If, instead of standard leads, unipolar extremity leads (Wilson's ordinary unipolar extremity leads,[4] or the author's augmented unipolar extremity leads [aV-leads][5]) are used, interpretation of axis deviation is simpler, because each unipolar extremity lead varies directly with the electrical axis of the heart.[6] But even with these leads, the explanation of physical changes, such as hypertrophy of the ventricles, in terms of the angle α is hard to grasp, especially when the angle α has negative values.

It was therefore felt that a graphic analysis by which the electrical activity of the ventricles could be interpreted in terms of the actual spread of the impulse through the muscle, rather than a mathematical calculation of the angle α at particular instants, might prove of value. We found the answer to this problem in the method we were using to analyze the patterns of unipolar leads.

Work done under the Martha M. Hall Foundation Fund for Research in Cardiovascular Disease, in memory of William Henry Hall.

From the Medical Division, Montefiore Hospital, New York, Dr. Louis Leiter, Chief; and the Department of Medicine, Lincoln Hospital, New York, Dr. Leander H. Shearer, Director.

Fifth in a series of papers on the application of unipolar leads to the study of problems in electrocardiography.

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*Fellow, Martha M. Hall Foundation.

†Although the electrical axis can, of course, be calculated for both the auricles and ventricles, in this paper the electrical axis of only the ventricles will be considered.

In brief, the principles underlying this method of interpretation of axis deviation and ventricular hypertrophy are the following: All unipolar electrocardiograms (whether extremity, precordial, or thoracic), irrespective of the location of the electrode, record the electrical activity of the heart as a whole, rather than favoring selective, small areas which may lie beneath the electrode.

An analogy may make this clearer: If a roentgenogram of the chest be taken, all the structures of the thorax are visualized, irrespective of whether the patient stands facing the x-ray tube (a-p position), or with his back to the tube (p-a position). The characteristics of the roentgenogram, however, will depend on many factors; for example, in the one taken in the first position, the heart will appear larger than in the second, because, in the first position, the heart was nearer to the x-ray tube.

Similarly, the characteristics of such electrocardiograms will also depend on several factors, namely: (a) The direction in which the electrical activity is spreading over the muscle, (b) the direction in which the regression of activity takes place, (c) the location of the electrode, (d) the distance of the electrode from the region of electrical activity, and (e) the size and shape of the ventricles.*[7]

The easiest way to grasp this concept is to begin with an explanation of the electrical activity of a simple muscle strip immersed in an extensive and uniform conducting medium, as recorded in the electrogram.†

To consider in more detail the five factors mentioned above: (a) and (b) *The Activation and Regression of Electrical Activity.*—It may be stated as a general rule that the wave of activation, which is quite rapid in muscle, has a (+) pole in the direction to which the impulse is spreading, and a (−) pole in the direction from which the impulse is passing[7, 8] (Fig. 1).

During the regression of electrical activity, which is a comparatively slow process, these conditions are reversed, and the (−) pole is in the direction to which the regression wave is passing (Fig. 1). Since muscle which has become activated does not stay in this state very long, the regression of activity starts soon after activation has begun, and, therefore, these two phases are going on simultaneously in different segments of the muscle mass for the greater period of the electrical activity in the muscle.

(c) *The influence of the Position of the Electrode.*—The influence of the position of the electrode on the individual deflections of the electrogram can also be seen in Fig. 1. In this example, the waves of activation and of regression travel in the same direction. An electrode at *F* will face the tail end of the wave of activation, and, consequently, will record

*For details of other less important factors, the reader is referred to the original paper of Macleod.[7]

†By definition, the electrogram is a record of leads from muscle strips or direct leads from the surface of the heart, in contradistinction to the electrocardiogram, which is taken with leads more or less distant from the heart.

(−) potentials throughout the period when the muscle is being activated. During the regression of activity, the electrode, also facing the tail end of the wave, now records a (+) deflection. An electrode at *H* will record an electrogram just the opposite to that at *F*, because, here, the electrode is always facing the oncoming waves of activation and regression.

With an electrode at *G* the following conditions hold: Up to the moment the wave of activation reaches the muscle immediately under *G*,

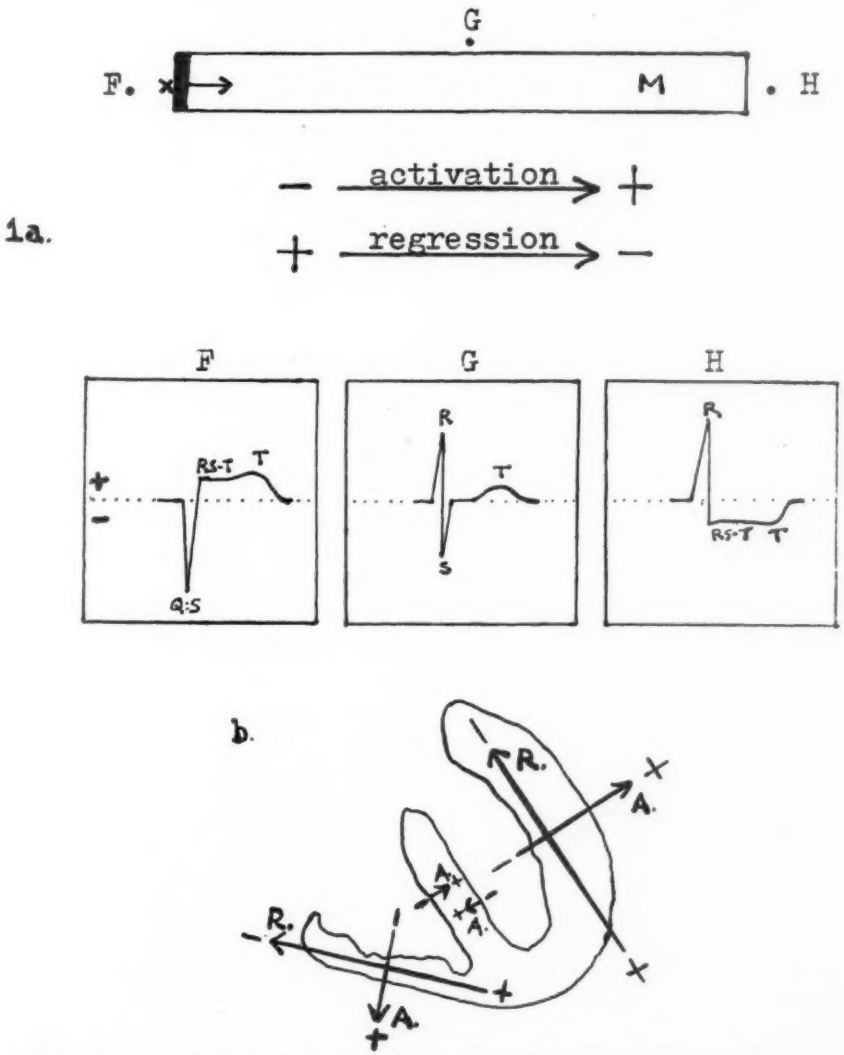

Fig. 1.—*a*, Electrical activity in a simple muscle strip immersed in an extensive and uniform conducting medium and recorded in the electrogram (after Macleod[2]). *M* = muscle strip, *x* = place of origin of the impulse, and *F*, *G*, *H* = electrograms which might be recorded if the electrodes were placed as in the sketch. It is assumed that, for each of the records, the other electrode (not shown) is so distant from the muscle that its potentials are negligible. The arrows indicate the direction in which the waves of activation and regression pass, and the polarities of the wave fronts.

b, Schematic representation of the paths of activation and of regression in the ventricles of the normal heart. *A* = activation, *R* = regression. The heart is shown in horizontal cross section as in Fig. 2*c*.

the electrode is facing the (+) pole of the wave, and a (+) deflection is recorded. During the remaining period of activation the electrode, facing the tail end of the wave, records a (−) deflection.

With respect to the regression of activity, up to the moment the regression wave reaches the muscle under *G*, the electrode has been facing its (−) front pole. This deflection is hidden within the QRS complex,[7] and the only portion of the regression wave clearly observed is that recorded during the latter stages of regression, when the electrode is facing its tail (+) end.

From the foregoing, the following conclusions may be drawn:

a. Although activation and regression of electrical activity go on simultaneously throughout the greater part of the electrical activity in the muscle, the QRS, in a general way, may be considered to be caused by the activation of the muscle, and the RS-T segment and the T wave to be caused by the regression of electrical activity.

b. The RS-T segment may lie above, on, or below the isoelectric line, and T may be (+) or (−), depending on the location of the electrode, other factors remaining equal.

c. When the waves of activation and regression travel along similar paths, the RS-T segment and T wave will tend to point in a direction opposite to the QRS.

d. *The Effect of the Distance Between the Electrode and the Region of Electrical Activity.*—The effect of the electrical activity on the electrode is inversely proportional to the square of the distance of the electrode from the source of the electrical activity.[7] Thus, if the electrode were moved from a point 3 cm., to one 6 cm., away from the region being activated, there would be a fourfold decrease in potential recorded, although the electrode was moved only twice as far from the active region.

The previously mentioned relations have been expressed mathematically,[7, 8] but need not be considered for the purposes of this paper.

e. *The Size and Shape of the Ventricles.*—These facts can be applied directly to the study of the human heart, if the following additional factors are taken into consideration and unipolar leads are used:*

1. The ventricles are not a simple muscle mass, but may be likened to two curved muscles joined at their adjacent ends by the interventricular septum to form an asymmetrical, cup-shaped muscle with its open end facing the head and right shoulder girdle[11] (Fig. 2).

The relations of the ventricles to the chest wall can be observed also in Fig. 2. It should be noted that practically all of the ventricular muscle lies to the left of the sternum; that the right ventricle lies in relation to the anterior chest wall; that the left auricle faces posteriorly (Fig. 2, *b*); and that the left ventricle actually overlies the diaphragm, and faces, for the most part, inferiorly.

*It is also assumed that the current produced within the heart is distributed uniformly throughout the body, and that the Einthoven triangle hypothesis is correct. Although this has been denied by some,[9] recent work serves to substantiate it.[10, 27]

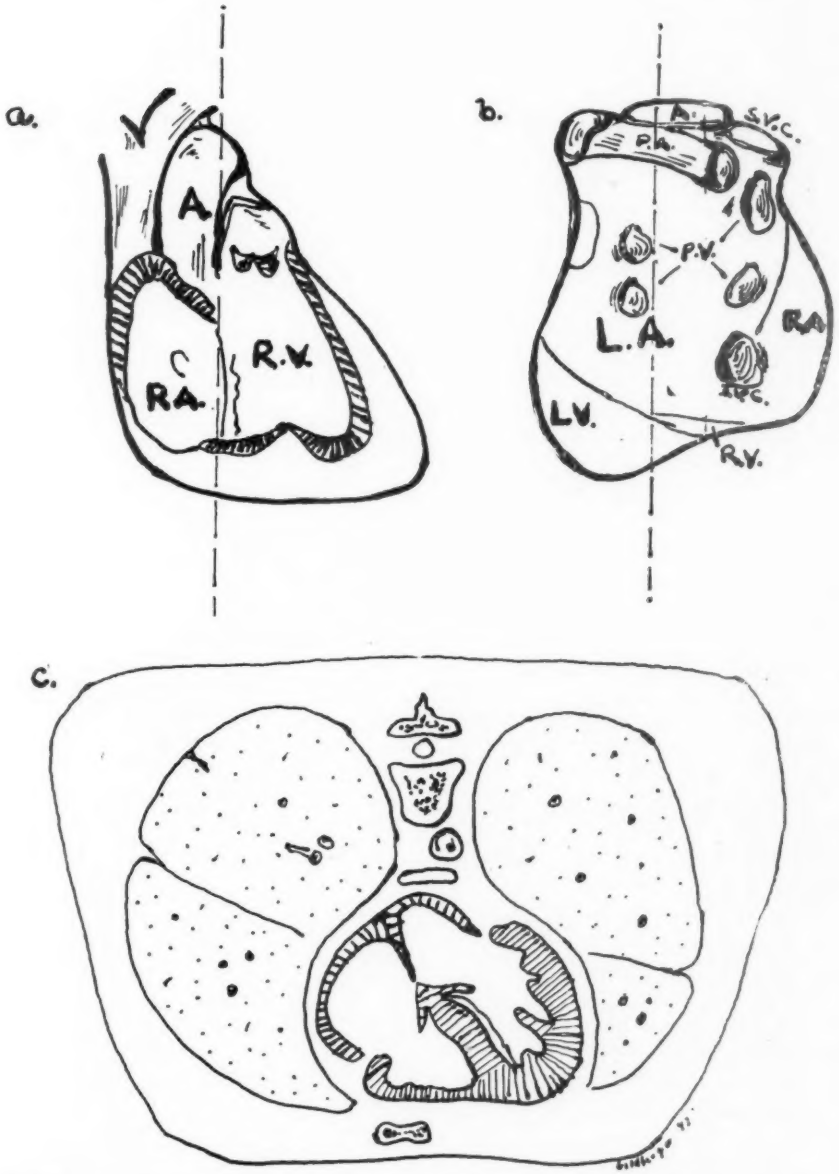

Fig. 2.—The relations of the heart to the thoracic cage. Vertical dotted lines represent the midline of the body. *A* = Aorta, *RA* = right atrium, *RV* = right ventricle, *LV* = left ventricle, *PA* = pulmonary artery at its bifurcation (at level of fifth dorsal vertebra), *PV* = pulmonary veins, *SVC* = superior vena cava, *IVC* = inferior vena cava, and *LA* = left atrium. *a*, Anterior view of the heart (after Cunningham[13]). The anterior walls of the right ventricle and right atrium and part of tricuspid valve have been removed.

b, Posterior view of the heart (after Cunningham[13]).

c, Cross section through chest at level of sternal end of fourth costal cartilage and eighth dorsal vertebra (after Eycleshymer and Shoemaker[21]).

2. Although the spread of the impulse is not even throughout the ventricles, the general direction of spread is from the subendocardial region of each ventricle outward to the epicardium of each ventricle.* Therefore, an electrode so placed that it faces the oncoming wave of activation in one of the ventricles is also facing, to some extent, the tail end of the activation wave in the other ventricle (Fig. 1, *b*).

3. A further complication arises from the fact that, normally, the thickness of the left ventricle is greater than that of the right. Consequently, the surface of muscle in the left ventricle in a state of partial activation or partial regression will tend to be greater than in the right ventricle; therefore, the electrical activity of the left ventricle will tend to dominate the electrocardiographic pattern.†

4. Unlike in the simple muscle strip, here the path of activation is different from the path of regression.[12] Therefore, T will tend to point in the same direction as QRS (Fig. 3).

MATERIAL AND METHOD

Although we have on file unipolar leads of more than 3,000 patients, in over 400 of whom multiple unipolar precordial leads were taken, for this particular study we selected 30 additional, adult subjects: 10 normal subjects; 10 patients with evidence of left ventricular preponderance in the electrocardiogram; and 10 with evidence of right ventricular preponderance.‡

In addition to the standard leads, the following unipolar leads (taken with the author's indifferent electrode of zero potential[5]) were used:

1. From the right arm (aVr lead).
2. From the left arm (aVl lead).
3. From the left leg (aVf lead).
4. R.S.Cl. lead, with the electrode at the apex of the supraclavicular region at the right midclavicular line.
5. Head lead, with the electrode at the angle of the left side of the mandible. In this connection, we conducted preliminary experiments and took records not only from various positions on the surface of the face and head, but also the tongue. All records were practically identical. Furthermore, when two electrodes were placed on the head and the potential difference measured, it was found that the string did not move at all, or minimal deflections were recorded. The head, therefore, for practical purposes, may, like the extremities, be considered as a volume conductor.
6. L.S.Cl. lead, similar to the R.S.Cl. lead.
7. R.U.Sc. lead from the base of the spine of the right scapula.
8. 2 R.M.Ax. lead, from the right axilla in the second intercostal space on the midaxillary line.
9. 2 R.M.Cl. lead, from the second intercostal space in the right midclavicular line.

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*It is assumed that the spread of activity from the subendocardial region of both sides of the septum inward serves to neutralize the effect of this activity on the electrocardiogram. However, recent work of ours[23] indicates that in many, if not in all, normal cases, the left side of the septum is activated before the right. This, if so, would serve to modify the initial QRS deflection only, and not the main ventricular deflection.

†There are no potential differences within a mass of fully active or inactive muscle. Therefore, such a region does not affect the electrocardiogram as long as this state continues.

‡Also see *Appendix*.

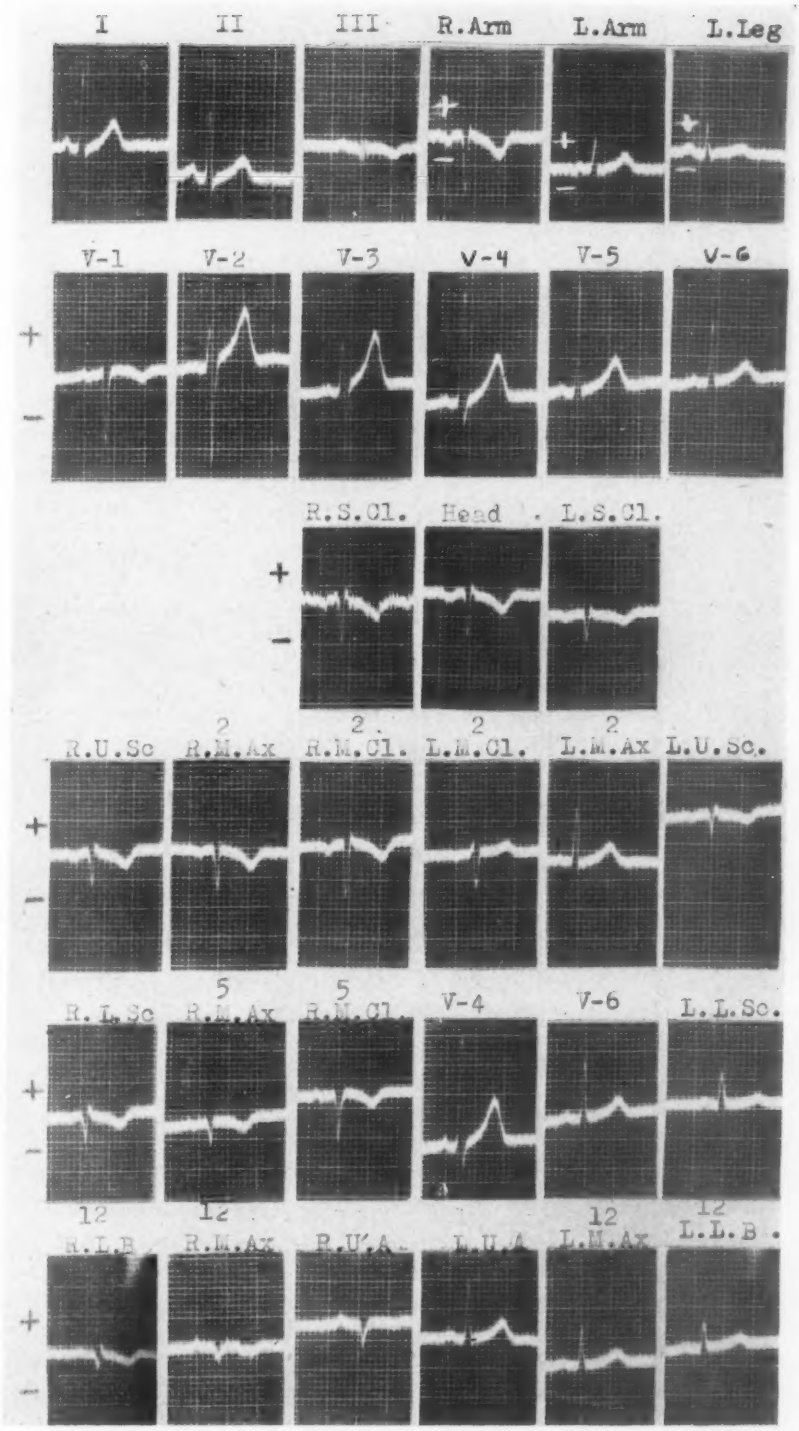

Fig. 3.—H. S., male, 26 years of age, normal.

For descriptions of symbols, refer to the text. The precordial leads V_4 and V_6 are repeated in most of the records. The unipolar leads are so taken that positivity is represented by an upward deflection.

10. 2 L.M.Cl. lead, similar to 2 R.M.Cl. lead.
11. 2 L.M.Ax. lead, similar to 2 R.M.Ax. lead.
12. L.U.Sc. lead, similar to R.U.Sc. lead.
13. R.L.Sc. lead, at angle of right scapula.
14. 5 R.M.Ax. lead, from the fifth intercostal space in the right midaxillary line.
15. 5 R.M.Cl. lead, from the fifth intercostal space in the right midclavicular line.
16. Lead V-1, with the electrode in the fourth intercostal space at the right border of the sternum.
17. Lead V-2, in the fourth intercostal space at the left border of the sternum.
18. Lead V-3, placed on the middle of a line joining the points of electrode application of leads V-2 and V-4.
19. Lead V-4 placed at the left midclavicular line in the fifth intercostal space.
20. Lead V-5, in the fifth intercostal space at the left anterior axillary line.
21. Lead V-6, at the left midaxillary line in the fifth intercostal space.
22. L.L.Sc. lead, at the angle of the left scapula.
23. 12 R.L.B. lead, in the twelfth intercostal space directly under the angle of the right scapula.
24. 12 R.M.Ax. lead, in twelfth intercostal space at right midaxillary line.
25. R.U.A. lead, on the right upper quadrant of the abdominal wall, at the level of the lowest costal cartilages and on the prolongation of the midclavicular line to the abdomen.
26. L.U.A. lead, similar to the R.U.A. lead.
27. L.M.Ax. lead, similar to 12 R.M.Ax. lead.
28. 12 L.L.B., on the back and similar to 12 R.L.B. lead.
29. On some of the patients the unipolar lead V-e, with the electrode over the xiphoid process, was taken. We found, as Wilson, et al.,[3, a] did, that the patterns in this lead were similar to those of lead V-1 or V-2.

Leads were taken with the patients sitting or in a semirecumbent position. The electrocardiograph was standardized so that a deflection in the record of 1 cm. was equivalent to one millivolt. Exceptions to this are found in the aV- leads, in which, although the electrocardiograph was standardized as usual, a 1.5 cm. deflection equals one millivolt.[5] Also, in taking some of the lower back leads, where the potentials were very small, the string was loosened.

RESULTS

The Normal Heart.—Ordinarily the long axis of the normal heart, "from the base to the apex, runs obliquely from behind, forward, and downward to the left."[13] Normal deviations may occur in two directions, depending on the size and shape of the thorax and the position of the diaphragm. In one type, the long axis of the heart is more or less vertical, whereas, in cases of heavy-chested persons with a high diaphragm, the long axis of the heart is likely to be quite oblique.

With this in mind, and from study of Figs. 1 and 2, the principles described above can be applied, and, on theoretical grounds alone, the following unipolar electrocardiographic patterns can be predicted:

a. Leads from the right arm, right shoulder girdle anteriorly and posteriorly, the head, left shoulder girdle posteriorly, and the right anterior part of the chest, including lead V-1, can be said to face the ventricular cavity. Therefore, the main QRS deflection should be (−).

b. Leads overlying or facing the epicardial surface of the left ventricle, i.e., from the left side of the precordium and left upper abdomen and left lower back should have a (+) main QRS deflection.

c. Leads overlying or facing the epicardial surface of the right ventricle, such as those over the lower midsternal region and right upper abdomen, should also have a (+) main QRS.

d. Transition zones may be expected in those regions which lie at the boundaries of those just described.

e. The T wave should tend to point in the same direction as the QRS.

Actual records correspond well to this, and may be divided into two types, determined by the location of the main transition zones. These zones are in the region of the left arm lead, the R.U.A. lead from the right upper abdominal wall, and the left leg lead.

To consider the left arm lead, we found that, although in all our records the upper left scapular lead was always (−), the left arm lead was either (+), biphasic, or (−) (with occasionally a [−] T), depending on whether the left arm was facing the epicardial surface of the left ventricle or the endocardium, which in turn depended on the position of the heart. When the long axis of the heart is oblique, the left arm lead faces the epicardium of the left ventricle and is therefore (+). With a vertical long axis, the left arm lead faces the endocardial surface of the ventricles and tends to be (−).

The second zone of transition was noted in the R.U.A. lead over the right upper abdominal wall. Here the potentials also varied from (+) to (−) Figs. 3 and 9, a. Although it might seem at first a paradox for a lead from the right upper abdominal wall, which faces the epicardial surface of the right ventricle (it also faces a portion of the left ventricle), to have a (−) QRS, this apparent discrepancy is easily explained when one remembers what was pointed out above, namely, that the electrical activity of the left ventricle is greater than that of the right, and that an electrode, although facing the oncoming (+) wave from within the right ventricle, at the same time is also facing the stronger (−) tail end of the wave passing outward through the main muscle mass of the left ventricle. As will be seen later with cases in which hypertrophy of the right ventricle was present, the patterns in this region of the body approach those theoretically anticipated.

When the heart is oblique the right upper abdominal lead faces more of the right ventricular surface and is (−); when the heart lies vertically the right upper abdominal lead faces more of the lower surface of the left ventricle, and its potential becomes slightly (+) (in children the [+] deflection may be marked).

The potentials of the left leg lead resemble those of the abdominal wall rather than those of the back; their appearance was intermedi-

ate between those of the right and left upper abdominal leads. They are not, therefore, as sensitive an index of the position of the heart as the right upper abdominal lead. Ordinarily the left leg lead faces varying aspects of the epicardial surfaces of both the right and left ventricles, also. With a vertical, normal heart, the left leg lead faces more of the left ventricle than of the right, and its potential is (+). When the normal heart lies obliquely, it faces more of the right ventricle than of the left, and its potential tends to be small and isoelectric, and even downward.

The right arm lead, always facing the endocardium, maintains its (−) potentials. There is, therefore, a reciprocal relation between the potentials of the left arm and left leg leads: When the heart lies vertically, the left leg lead faces the left ventricle and is upright; the left arm lead, facing the endocardium, has a downward potential. When the heart lies obliquely, it is the left arm lead which faces the left ventricle, and is upright; the left leg lead, facing the small right ventricle, is downward.

These results can also be interpreted in terms of standard leads. Although each of the standard leads represents the algebraic difference between the potentials of the two extremities being used,[6, 14] for the purposes of this paper we can state that Lead I resembles the left arm lead and Lead III resembles the left leg lead, especially if Leads II and III are similar. Lead II, of course, equals the sum of Leads I and III.

Therefore, when the long axis of the heart is vertical, the left leg lead, facing the left ventricular surface, and Lead III will be upright; the left arm lead, facing the endocardium, and Lead I will be downward. This pattern has been arbitrarily designated as right axis deviation.

When the long axis of the heart is oblique, it is the left arm lead which faces the left ventricular surface, and it and Lead I will be upright; and the left leg lead, facing the right ventricular surface, and Lead III will tend to be isoelectric or downward. This has been arbitrarily designated as no axis deviation or left axis deviation, respectively.

When the left arm and left leg potentials are about equal, as they often are, Lead III will be isoelectric (Lead III equals the left arm minus the left leg potentials).

To summarize: the electrical axis in the normal electrocardiogram is determined by the position of the heart within the thorax, and, more particularly, by the relations of the left ventricular surface to the left arm and left leg leads. A vertical heart produces the patterns arbitrarily designated as right axis deviation; an oblique heart produces the patterns arbitrarily designated as a normal electrical axis and left axis deviation.

A word may be said about the precordial leads. It can be seen in Fig. 3 that lead V-1 is similar to leads from the right upper chest, and leads V-5 and V-6 are similar to leads from the left upper body anteriorly. Thus, the biphasic leads V-2, V-3, and V-4 may also be considered

transitional leads, although in the normal their patterns do not vary to any extent with variations in the position of the heart.

Left Ventricular Hypertrophy.—When hypertrophy of the left ventricle occurs due to hypertension or other causes, the following factors tend to make the electrocardiogram deviate from normal: (a) The left ventricle enlarges anteriorly, to the left, and posteriorly. With this, the apex is usually displaced both downward and to the left, causing the long axis of the heart to be more oblique than it is normally; (b) The greatly enlarged left ventricle serves to further enhance its dominance of the electrical activity of the ventricles.

With these additional factors in mind, theoretical analysis, similar to that used for the normal heart, allows the following predictions:

1. Because of the marked obliquity of the heart, not only the left arm lead, but leads from the head and supraclavicular regions should tend to face the epicardial surface of the left ventricle, and record (+) potentials instead of being (−).

2. Due to the greatly enlarged left ventricle and its increased electrical activity, leads from a large area of the left upper portion of the trunk facing the left ventricle should exhibit large (+) potentials and the standard leads should also have large amplitudes; leads facing the epicardial surface of the right ventricle (and consequently the endocardium of the left ventricle) should be definitely (−). Actually, these conditions prevail (Figs. 4 and 5).

In Fig. 4, from a 73-year-old white man with hypertension, although the right arm lead (aVr lead) shows a (−) potential, in the right supraclavicular region (R.S.Cl. lead) the potential is biphasic and partly (+), and it is (+) at the head and at the left supraclavicular region (L.S.Cl. lead). Leads from the left upper trunk anteriorly and posteriorly, including the L.U.Sc. lead from the base of the spine of the left scapula, also have a (+) potential. All the leads from the right side of the body, anteriorly and posteriorly, on the other hand, have a (−) main QRS.

It should be noted that leads from the left abdominal wall, angle of the left scapula, and left lower back have a (−) main QRS. This is further indication of the marked obliquity of the heart, and of the fact that the main muscle mass of the hypertrophied left ventricle now points posteriorly in the direction of the left shoulder girdle, rather than inferiorly. Therefore, with leads from the lower left side of the trunk and the left leg, the main body of the wave of activation will be moving away from them, and QRS will be (−), even though the wave is passing outward to the epicardium.

The precordial leads are very characteristic. Those near the sternum are like leads from the right side of the body, and those near the apex are like those from the left side of the body. Changes in the RS-T segment and T wave can be better analyzed in the following record, Fig. 5, from a 48-year-old white woman with a blood pressure of 250/150.

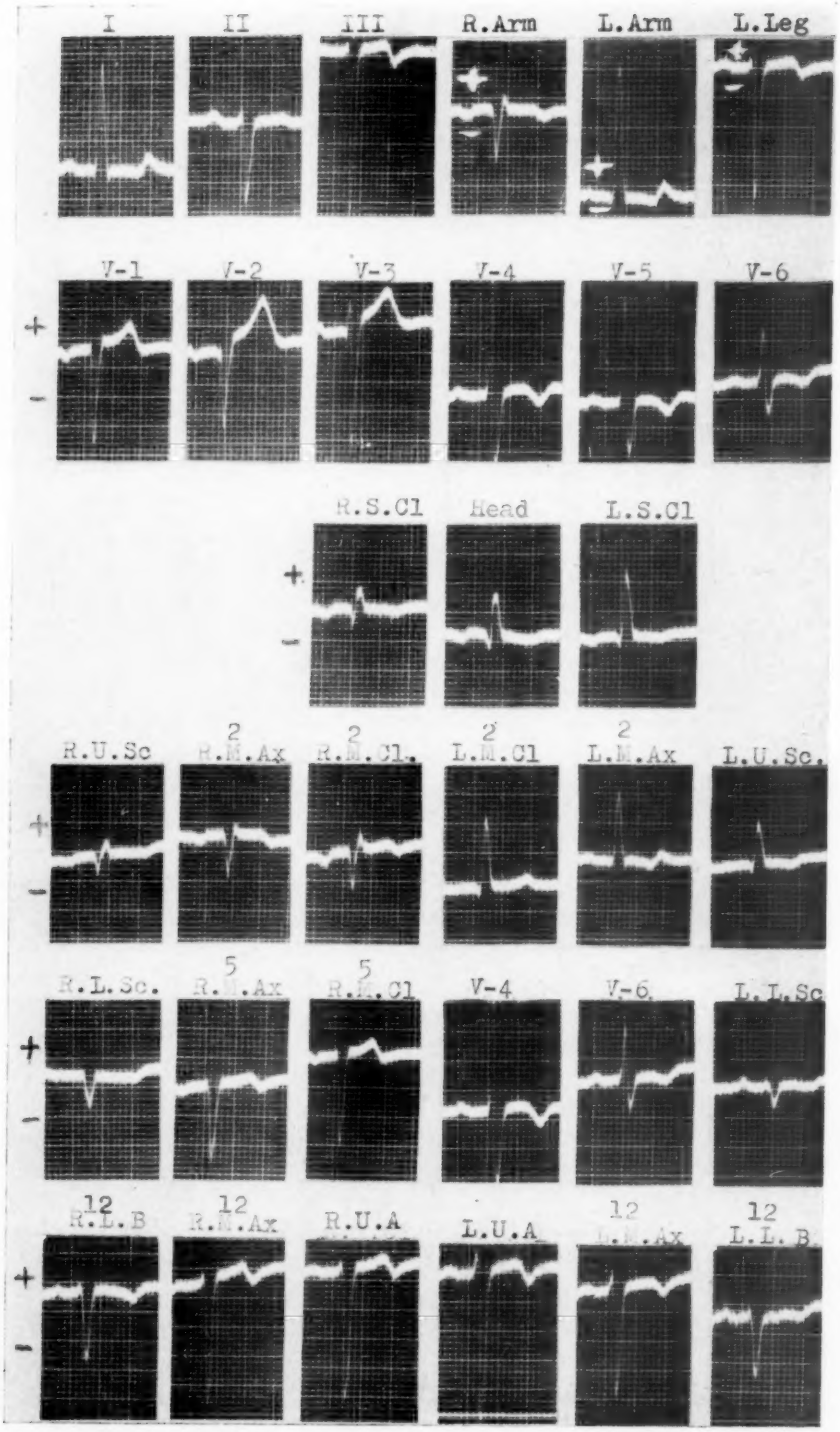

Fig. 4.—M. Z., male, 73 years of age, hypertensive cardiovascular disease. Patient had no complaints referable to the heart, and was receiving no medication.

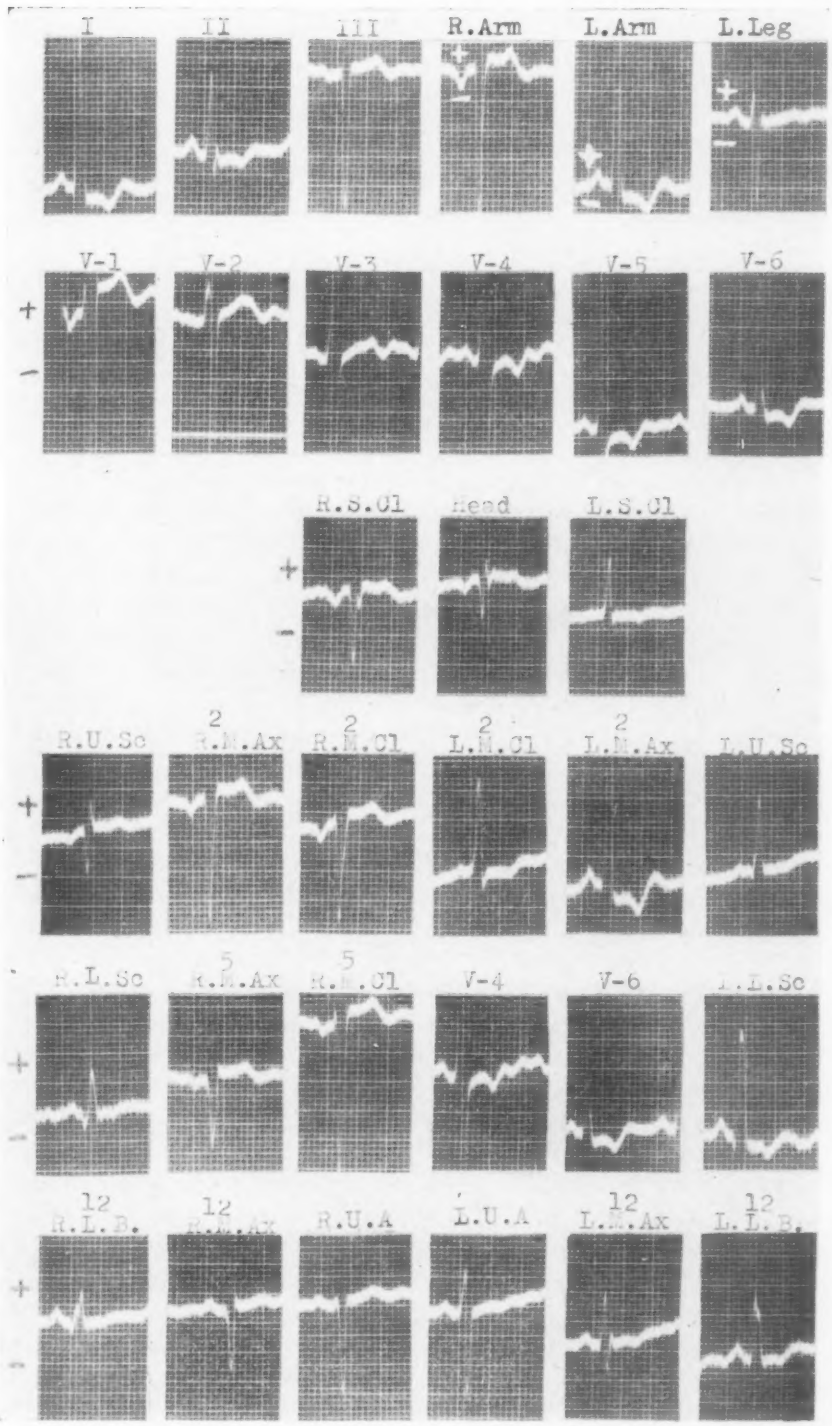

Fig. 5.—M. G., female, 48 years of age, hypertensive cardiovascular disease. Blood pressure, 250/150; no medication given.

One perceives that the T wave in practically all the leads points in a direction opposite to that of the QRS, and that, along with this, the RS-T segment is no longer isoelectric, but has also deviated in a direction opposite to the QRS. Although many reasons for this have been proposed,[15, 16] an adequate explanation is not yet available other than that the changes do not indicate myocardial damage. A more detailed interpretation of these changes will be presented in another paper.[23]

In this case the QRS patterns are, in the main, similar to those in Fig. 4. Here the long axis of the heart is less oblique, and although the left supraclavicular lead (L.S.Cl. lead) has become (+), the head and R.S.Cl. leads remain (−). Posteriorly, leads from the right lower back and all the leads from the left side of the back are (+), which is also a sign that the obliquity of the heart is less than in the case illustrated in Fig. 4.

Fig. 8 represents another interesting case in which marked left ventricular hypertrophy was present in association with right ventricular hypertrophy. Note the presence of right axis deviation in spite of the left ventricular hypertrophy which was present.

The extremity leads, as in the normal, occupy transition zones of potential, and variations are due to the position of the heart in the chest and *not* primarily to the left ventricular hypertrophy. Usually, the heart lies obliquely, and this, as in the normal, results in left axis deviation. However, because the obliquity is more marked than normal, the left leg lead, facing the right ventricle, becomes deeply (−). The right arm potentials usually remain (−), although, with marked shift of the long axis, these too become biphasic. It is this, as has been previously reported,[6] which is the cause of the two types of patterns in left ventricular hypertrophy which Barnes has described.[15] In the first type, the right arm lead is (−), and Leads I and II are similar; when the right arm becomes biphasic, Leads II and III become similar.* Figs. 4 and 5 illustrate these two types.

When due to other factors, such as abnormalities of the thoracic cage, concomitant enlargement of the right ventricle, etc., the long axis of the heart tends to remain vertical, and the extremity leads will show the normal patterns, without axis deviation, in spite of the ventricular hypertrophy. In such cases, however, the characteristic (+) QRS in leads over the hypertrophied left ventricle, and the (−) QRS in leads facing the right ventricle, along with high voltage in the standard leads and RS-T and T-wave changes, are often observed.

Cases of left ventricular hypertrophy have been described which show only marked left axis deviation.† In our cases of this type, the marked obliquity of the heart produced not only the patterns of left axis deviation, but, because of the large left ventricle, the left upper scapular lead (L.U.Sc. lead), which in the normal is always (−), had become

*This may also occur in a markedly oblique normal heart.
†A downward Lead II and III.

(+)* (Fig. 9, *b*). To summarize, then, the main features of the patterns in hypertrophy of the left ventricle are:

1. The QRS in leads over the hypertrophied left ventricle, particularly the precordial leads V-4, V-5, and V-6, are large and (+), and high voltage in the standard leads is often observed.

2. Leads facing the small right ventricle, such as the precordial leads V-1 and V-2 and the R.U.A. lead from the right upper abdominal wall, are (−).

3. With this may be associated characteristic RS-T and T-wave patterns in which they deviate in a direction opposite to the QRS.†

4. The unipolar extremity and standard leads may exhibit left axis deviation or normal or even right axis deviation, depending on the long axis of the heart, just as in the normal. Usually the long axis of the heart is quite oblique, and left axis deviation is present (high left arm and Lead I potentials, and deep left leg and Lead III potentials). When the obliquity is very marked, Lead II also points downward.

5. In cases in which the obliquity of the long axis of the heart causes left axis deviation without RS-T and T changes, the left ventricular hypertrophy causes the entire left shoulder girdle, including the left upper scapular lead (L.U.Sc. lead), to be (+). This does not occur in the normal oblique heart.

Right Ventricular Hypertrophy.—With right ventricular hypertrophy the following factors tend to make the electrocardiogram deviate from normal:

a. With moderate right ventricular hypertrophy there may not be any apparent change in the contour and position of the heart.[24, 25] With marked enlargement, the right ventricle bulges anteriorly, obliterating the retrosternal space, and the apex of the heart is displaced horizontally to the left. Occasionally there occurs the so-called triangular heart.[24] The effect of this on the long axis of the heart is variable, but it usually remains more or less vertical.

b. The increased mass of the right ventricle tends to counterbalance the electrical activity of the left ventricle. Thus, again on theoretical analysis, the following unipolar patterns may be predicted:

1. Because of the vertical long axis of the heart, leads from the head and both shoulder girdles should be (−), and right axis deviation should be present, as in the normal vertical heart.

2. Leads facing the epicardial surface of the hypertrophied right ventricle, such as those over the right lower anterior part of the chest and midsternal region, and both sides of the abdominal wall, should have a (+) QRS.‡ Study of actual records confirms this.

Fig. 6 is a record from a 43-year-old white woman with an interauricular septal defect and mitral stenosis (Lutembacher syndrome).

*See *Appendix*.

†The undulating RS-T and T may be likened to a roller coaster. The presence of this pattern does not necessarily indicate ventricular hypertrophy.

‡The vertical position of the heart also contributes to the (+) abdominal wall potentials.

She had mild decompensation, for which she had been digitalized. Note the (+) main QRS deflections in leads from the lower right anterior chest and right upper abdomen, and the (−) QRS from leads from the head, left upper chest, and both shoulder girdles.

In the precordial leads, the (+) potential of lead CF_2 is typical. Usually the first precordial lead (here CF_1 with the left leg as the indifferent electrode) also has a large (+) deflection, but in this case it resembled the other leads from the right upper anterior chest wall. This, however, may be due to the effect of the potentials of the left leg.

Over the left side of the precordium, as lead V-6, the potentials from the right and left ventricles tend to balance each other, and a biphasic complex is recorded. When the left ventricle is small compared to the right ventricle, the leads over the left side of the precordium, facing the tail end of the wave passing outward through the large ventricle, will record (−) deflections as in leads from the left shoulder girdle. In this case, digitalis probably contributed somewhat to the RS-T and T deviations[17] which, however, are often observed with right ventricular hypertrophy.*

In the extremity leads, because of the vertical long axis of the heart, the left arm lead faces the endocardium and is consistently (−). The right arm lead usually is (−), but when the long axis of the heart is very vertical, the right arm tends to face the epicardium of the right ventricle as well as the endocardium, and becomes biphasic. It is this, as has been previously reported,[6] which is the cause of the two types of patterns in right ventricular hypertrophy which Barnes has described.[15] In the more common type, the right arm is (−) and Leads I and II are similar. When the right arm lead becomes biphasic, Leads II and III become similar (Figs. 6 and 9, *d*).

Because of the vertical position of the heart, the left leg might be expected to face the epicardium of the left ventricle as in the normal vertical heart. If the left ventricle is small compared to the right ventricle, the left leg lead, which faces the left ventricle, will tend to be isoelectric. This, as Wilson and his associates[3a] have pointed out, results in deep S waves in the three standard leads, rather than right axis deviation. An example of this is shown in Fig. 9, *e*.

Isolated right ventricular hypertrophy is, however, much less common than cases in which there is concomitant hypertrophy of both the right and left ventricles. In fact, it has been stated that the most frequent cause of right ventricular hypertrophy is an antecedent hypertrophy of the left ventricle.[26] In such cases, the electrocardiographic patterns are not as characteristic as the one just described.

Fig. 7 illustrates such a case, that of an 80-year-old white woman with emphysema and hypertension. She was not receiving any medication. Note how the features of both right and left ventricular hypertrophy are present. The precordial leads are suggestive of left ven-

*Here again, the presence of the RS-T and T changes does not necessarily indicate ventricular hypertrophy.

tricular hypertrophy. But the downward T_2 and T_3 are usually seen with right ventricular hypertrophy,[18] as are the (−) potentials of the head and both shoulder girdles and the (+) QRS and (−) T of the R.U.A. lead from the right upper abdominal wall. In this connection, an important fact should be noted: In all our cases of right ventricular hypertrophy, the R.U.A. lead from the right upper abdominal wall

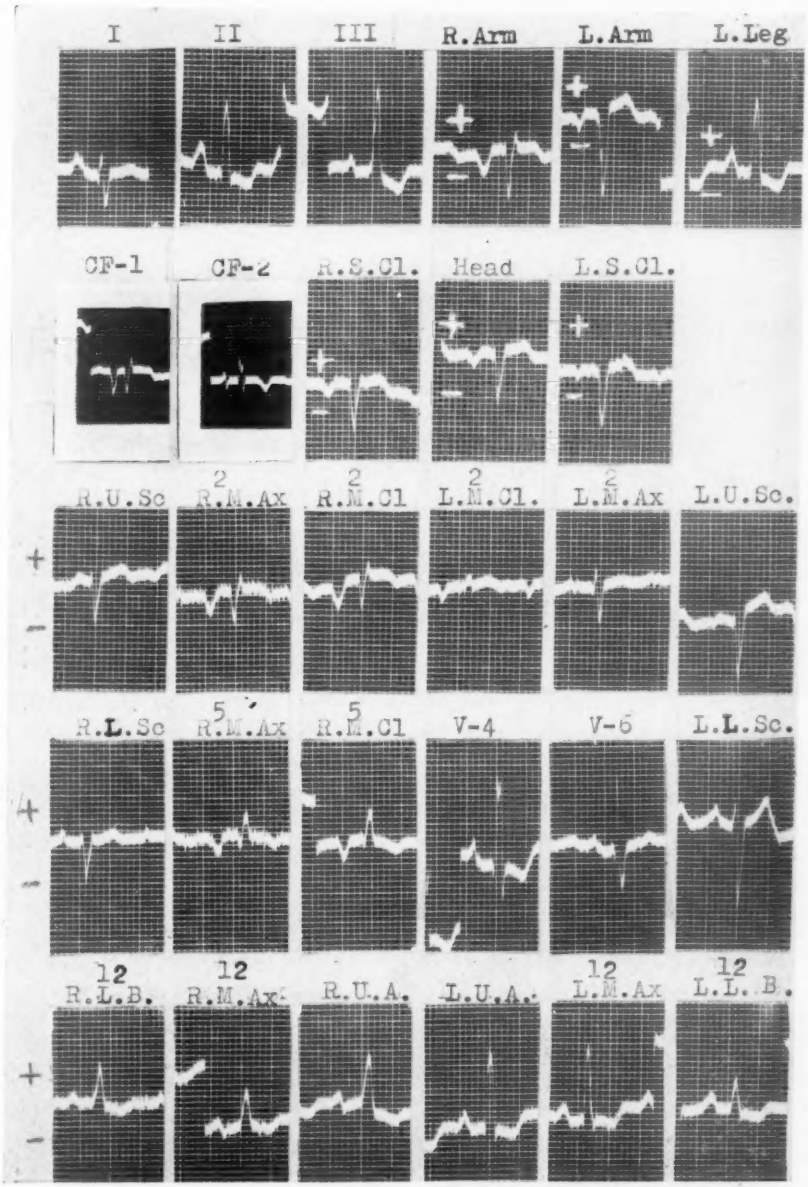

Fig. 6.—P. B., female, 43 years of age, interauricular septum defect and mitral stenosis (Lutembacher syndrome). Patient had mild decompensation, for which she had been digitalized. Photographs of the precordial leads CF_1 and CF_2, taken with the leg as the indifferent electrode, are included.

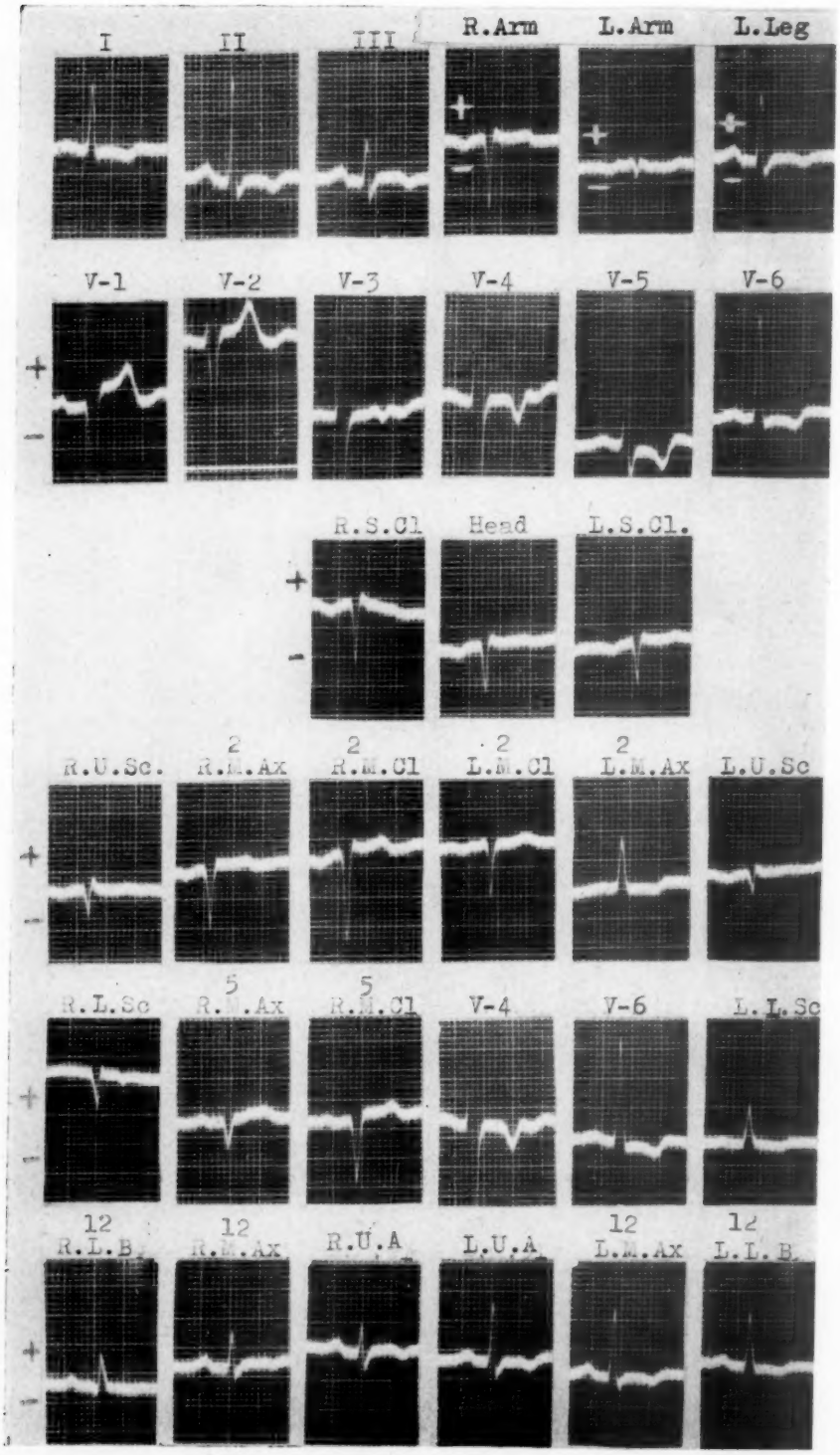

Fig. 7.—T. A., female, 80 years of age. Emphysema and hypertensive cardiovascular disease. Patient was not receiving any medication.

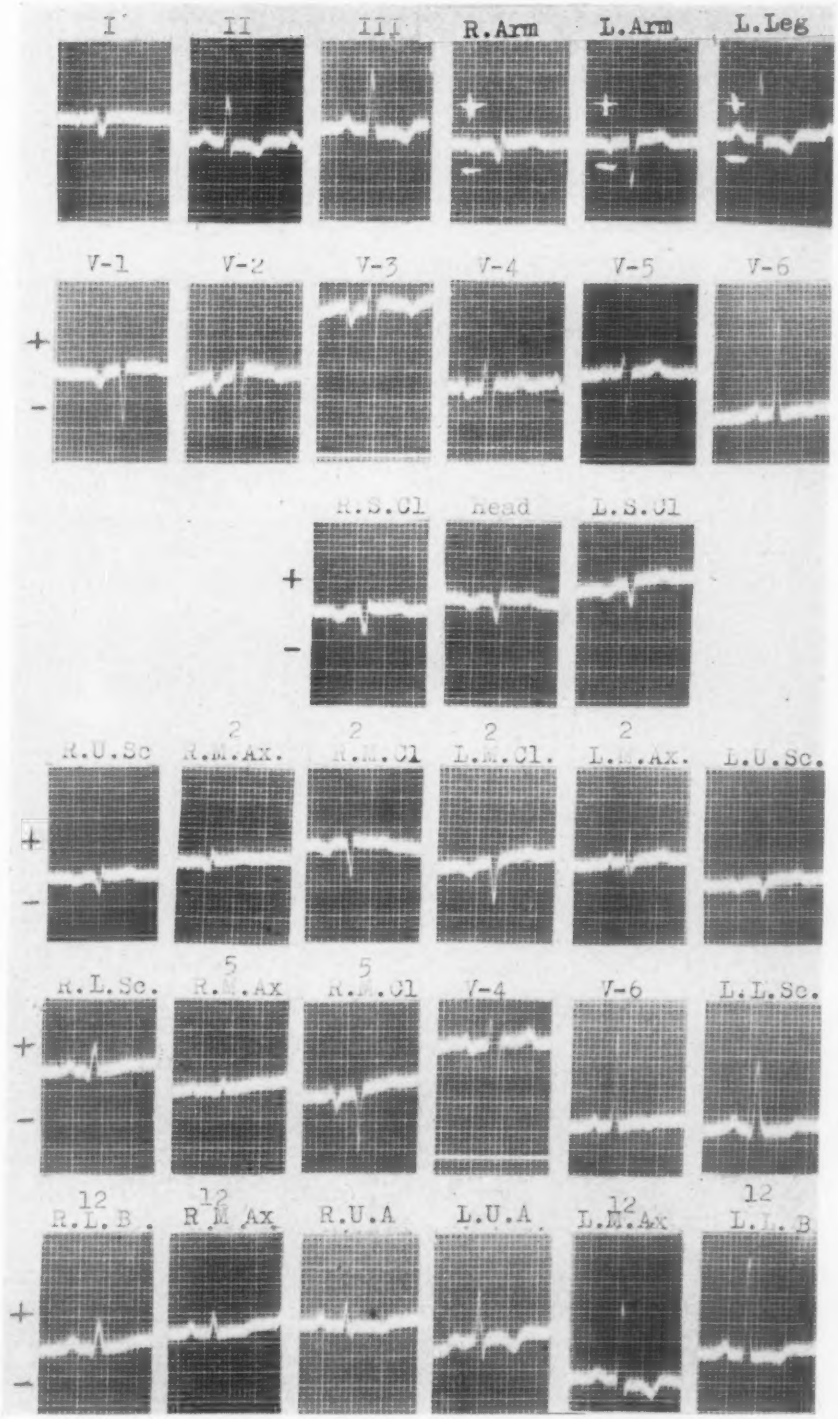

Fig. 8.—C. D., colored, male, 45 years of age. Hypertensive cardiovascular disease and kyphoscoliosis, and latent syphilis. Patient had moderate right heart failure, for which he had been digitalized. Blood pressure, 180/125.

was (+), irrespective of whether left ventricular hypertrophy was or was not present. In all our cases of isolated left ventricular hypertrophy, this lead was (−) or isoelectric.

Cases of right ventricular hypertrophy have been described in which there was only right axis deviation without RS-T and T-wave changes. In our cases of this type, the vertical, long axis of the heart produced

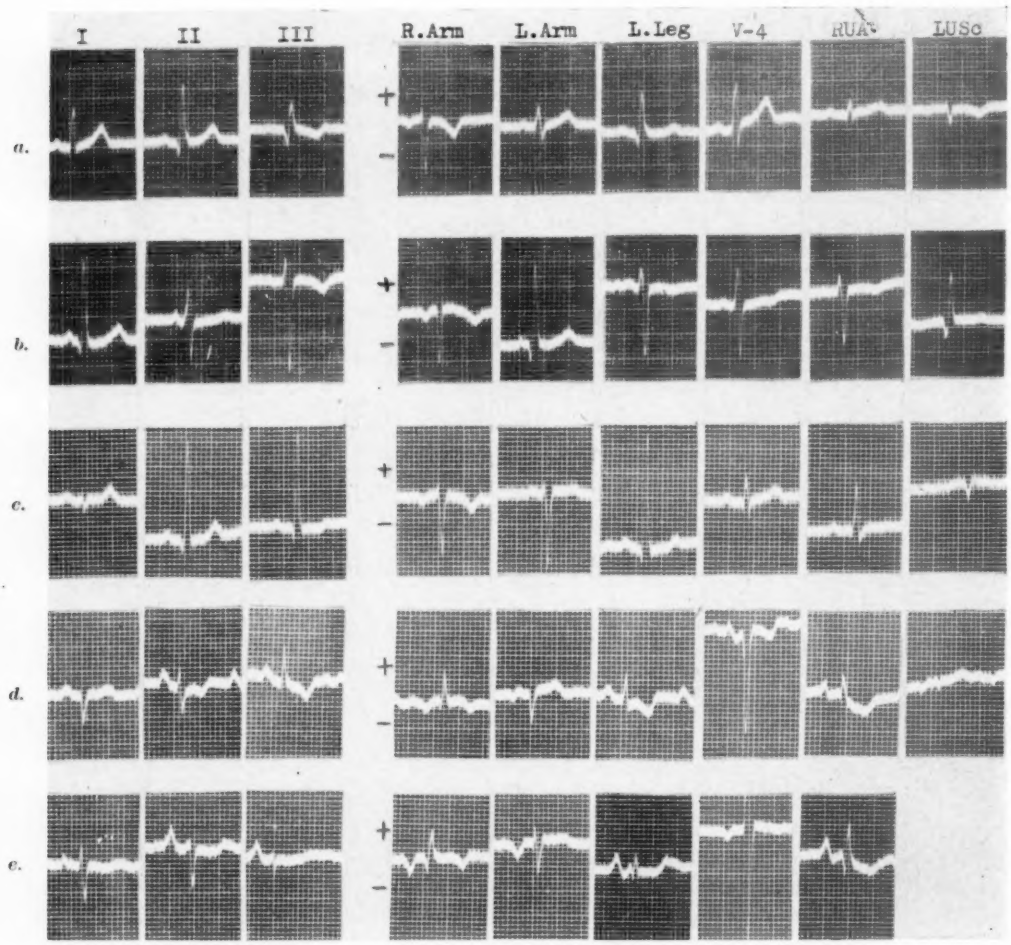

Fig. 9.—*a*, J. J., male, 26 years of age, normal; *b*, R. W., female, 46 years of age, hypertensive cardiovascular disease; *c*, R. G., female, 41 years of age, chronic fibroid pulmonary tuberculosis; *d*, E. C., female, 48 years of age, chronic asthma; and *e*, B. K. male, 59 years of age, chronic cor pulmonale (the precordial lead is CF_4).

not only the pattern of right axis deviation (deep left arm and Lead I potentials, and high left leg and Lead III potentials), but, because of the large right ventricle, the R.U.A. lead from the right upper abdominal wall, facing the right ventricle, had become highly (+), which is not observed normally* (Fig. 9, *c*).

*See *Appendix*.

To summarize, right ventricular hypertrophy may cause the following electrocardiographic patterns:

1. Leads facing the enlarged right ventricle, especially the R.U.A. lead from the right upper abdominal wall, are characteristically (+). A (+) QRS is also often observed in precordial leads from the midsternal region, and standard leads may also have high voltage.

2. Leads from the left side of the precordium, facing the left ventricle, are biphasic and may be (−) if the left ventricle is comparatively small.

3. With this, there are often associated RS-T and T-wave deviations in a direction opposite to the QRS.

4. The unipolar extremity and standard leads may exhibit right axis deviation, or no axis deviation, or deep S waves in the three standard leads,* depending on the long axis of the heart. Usually the heart is vertical and, as in the normal, the left leg lead faces the epicardial surface of the left ventricle and the left arm lead, the endocardium, producing deep left arm and Lead I potentials and high left leg and Lead III potentials (right axis deviation).

5. The presence of left ventricular hypertrophy in association with the right ventricular hypertrophy causes variations in the long axis of the heart (and therefore changes in axis deviation), and the precordial leads resemble those observed in uncomplicated left ventricular hypertrophy. However, in such cases, as well as in cases in which the hypertrophied right ventricle causes changes in axis deviation only, the right upper abdominal lead (R.U.A. lead), which faces the right ventricle, is always (+), indicating the presence of hypertrophy of the right ventricle.

DISCUSSION

The principle of considering the electrical activity of the heart as a whole is essentially that developed by Wilson and his associates some years ago.[7, 8] However, the fact that leads taken with the exploring electrode on the exposed surface of the heart (direct leads), or over a saline soaked gauze pad overlying the heart (semidirect leads), or on the thorax over the heart give records which are qualitatively similar, except that the amplitude of the deflections decreases as the electrode is moved farther from the heart, have led them to postulate the concept that precordial leads preferentially depict events in that region of the heart immediately underlying the electrode, that the main (−) deflection of the QRS complex begins when the muscle underlying the electrode becomes activated, and that the patterns of axis deviation depend on whether the potentials from the epicardial surfaces of the right ventricle and left ventricle are transmitted to either the left arm and left leg respectively, or vice versa.

*Left axis deviation will not occur even if the heart is oblique because the left leg lead, facing the large right ventricle in such a case, will be upright instead of small.

We feel that this explanation is too limited in scope, however. In the first place, the distance from the surface of the right and left ventricles to the chest wall is sufficiently great to minimize the effects of any one small area of the heart on the electrode. Secondly, the orderly sequence of unipolar lead patterns over the entire surface of the body, and the similarities between precordial leads and leads from adjacent regions of the chest appear to indicate that one mechanism is responsible for all the patterns. If this is not so, at what point does the electrode cease favoring selective potentials from the underlying muscle, and begin to record the electrical activity of the ventricles as a whole?

With respect to Groedel's ideas[19] about partial thoracic electrocardiograms in which he claims to have isolated the electrocardiograms from the right and left ventricles, the criticism leveled at the above concepts more strongly apply. Furthermore, our records do not support Groedel's ideas.

The concepts of Katz and his associates,[20, a, b] in which complex batteries spread throughout the ventricles, is unnecessarily complex, we think.

Although we have emphasized the changes in axis deviation in terms of shifts in the long axis of the heart around an anteroposterior axis, experimental observations have shown that, in the normal, there occurs, along with the shift in the long axis, concomitant rotation of the ventricles around the long axis.* The relations between the changes in the long axis and the direction of rotation of the ventricles around the long axis are usually constant. Thus, when the long axis of the heart becomes more vertical, the anterior surface of the right ventricle tends to rotate to the left; and when the long axis becomes oblique, rotation of the right ventricle is to the right.[22]

CONCLUSIONS

The following principles, which serve to explain the electrical activity recorded from a simple muscle strip, are applicable to the study of the electrical activity of the human heart as recorded by unipolar and standard leads.

1. When the electrical activity of the heart is studied with multiple unipolar leads on the surface of the body, the electrocardiograms obtained are observed to vary in an orderly sequence. These variations are dependent on: (a) the location of the electrode, (b) the size, shape, and position of the ventricles, (c) the direction in which the wave of activation spreads in the muscle, and the direction of the regression wave, and (d) the distance of the electrode from the source of electrical activity.

2. Irrespective of the location of an electrode on the surface of the body, it records potentials from the both ventricles, rather than preferentially recording potentials from any one area of the heart.

*There may also be rotation around a transverse axis and perhaps other axes.

3. In the human heart, which resembles an asymmetrical cup with its open end facing the head and right shoulder girdle, the spread of electrical activity is from within outward, in both ventricles. However, since the mass of the left ventricle is greater than the right, its electrical activity tends to dominate the electrocardiogram.

4. The unipolar electrocardiogram depends, therefore, primarily on the relation of the electrode to the endocardium or the epicardium; and if the electrode faces the epicardium, the relative sizes of the ventricles must also be taken into account.

5. In the normal heart, leads from the right upper region of the body, including the right arm lead and the precordial lead V-1, face the endocardium, and are (−). Leads facing the epicardium of the left ventricle, as precordial leads V-5 and V-6, are (+). The left arm lead, the left leg lead, and the right upper abdominal wall lead are situated in transitional zones of potential, however. The polarities of these leads often vary greatly with changes in the long axis of the heart.

When the heart lies vertically, the left leg lead faces the surface of the left ventricle, and its potential, as well as that of Lead III, which resembles it, is upward. The left arm lead faces the endocardium, and it and Lead I, which resembles it, are downward. This pattern has been arbitrarily designated as right axis deviation.

When the heart is oblique, it is the left arm lead which faces the left ventricular surface. Therefore, it and Lead I are now upright. The left leg lead faces the right ventricular surface, and it and Lead III tend to be small or even downward. The pattern has been arbitrarily designated as that of a normal electrical axis or of left axis deviation, depending on whether Lead III is upright or downward.

It may therefore be said that the relations of the surface of the left ventricle to either the left arm lead or the left leg lead govern the patterns known as axis deviation.

7. Because the paths of activation and of regression of the electrical activity in the normal heart are different, the T wave points in the same direction in practically all unipolar leads.

8. When hypertrophy of the left ventricle occurs, the obliquity of the heart causes the patterns of left axis deviation, just as in the normal. However, the left axis deviation is often marked (Lead II, as well as Lead III, is downward). Also, in such cases, because of the hypertrophy of the left ventricle, the left upper scapular lead (L.U.Sc. lead) becomes (+).

If for any reason the long axis of the heart becomes or remains vertical, normal or even right axis deviation may be seen. Along with the changes in axis deviation, RS-T and T deviations in a direction opposite to the QRS are often seen in practically all leads, although the presence of the RS-T and T deviations does not necessarily indicate ventricular hypertrophy. Along with this there may be the following additional signs of enlargement of the left ventricle: large (+) deflections in leads facing the hypertrophied left ventricle, as from the left

side of the chest, especially precordial leads V-4, V-5, and V-6, and high voltage in the standard leads; and deeply (−) deflections in leads facing the small right ventricle, as from over the midsternal region and the right upper abdominal wall (R.U.A. lead).

9. With hypertrophy of the right ventricle, the heart tends to lie vertically and right axis deviation occurs as in the normal. If the left ventricle is small compared to the right, the left leg lead, facing the left ventricle because of the vertical position of the heart, will also be small in amplitude. This may result in deep S waves in the standard leads, rather than the pattern of right axis deviation. There may also be RS-T and T deviations in practically all leads (although, here again, their presence is not necessarily an indication of ventricular hypertrophy), and the following additional signs of enlargement of the right ventricle: (+) deflections from leads facing the hypertrophied right ventricle, such as the right upper abdominal lead (R.U.A. lead), and often the precordial leads from the midsternal region; and biphasic, small, or even downward deflections from leads over the left side of the chest, which face the small left ventricle.

When there is concomitant left ventricular hypertrophy, the precordial leads record the characteristics of the left ventricular hypertrophy. The right upper abdominal lead, facing the hypertrophied right ventricle, however, is (+) even in such cases.

To conclude, when the normal and hypertrophied heart is studied by means of unipolar leads taken over the surface of the entire body, it becomes evident that, although leads near the heart and from the right shoulder girdle have a fairly fixed pattern, the left arm and left leg leads occupy transition zones of potential, and the unipolar extremity and standard leads are influenced not so much by the size of the heart as by its position in the thorax. It is for this reason that chest leads offer a more suitable index of ventricular hypertrophy than the extremity leads. However, the multiple precordial leads in use today are only partially successful in recording evidence of right ventricular hypertrophy, especially when it is associated with some degree of left ventricular hypertrophy. Our incidental observation of the constancy of the pattern of the right upper abdominal unipolar lead, particularly in such cases, makes us suggest that it may have use as an index of right ventricular hypertrophy. Similarly, the left upper scapular unipolar lead may have value in diagnosing left ventricular hypertrophy when only left axis deviation is present in the standard and precordial leads.

SUMMARY

1. The physiologic principles by which unipolar leads can be interpreted are described.

2. The patterns of unipolar surface potentials over the body in the normal subject and in cases of right and left ventricular hypertrophy are illustrated.

3. A nonmathematical approach to the problem of axis deviation is presented.

4. The advantage of leads close to the heart over extremity leads in the diagnosis of ventricular hypertrophy is emphasized.

5. The use of the right upper abdominal unipolar lead (R.U.A. lead) as an index of right ventricular hypertrophy, and of the left upper scapular unipolar lead (L.U.Sc. lead) in the diagnosis of hypertrophy of the left ventricle is briefly described.

APPENDIX

Our observations on the use of the right upper abdominal and left upper scapular unipolar leads have not been confined to the small series of cases described in this paper. We have begun to collect a large series of these leads in order to establish exact standards for their values. Judging from our preliminary observations, an amplitude of more than (+) or (−) 4 mm. in an adult is to be considered abnormal. We have not as yet developed standards for children, in whom the amplitudes of these leads are larger than in adults.

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ADDENDUM

Although study of Fig. 1 led us, at first, to think that the T-wave changes often observed in cases of ventricular hypertrophy were indicative of the fact that the paths of activation and of regression were now similar, we no longer believe that this is the only explanation possible. Recent observations of ours which have been made since this paper was written[23] suggest that, in some of the cases of ventricular hypertrophy in which T-wave changes are present, they are due not to the hypertrophy but to the position of the heart, in a manner similar to that affecting the QRS complex. Thus, when the heart is vertical and markedly rotated clockwise around its long axis, a downward T_2 and T_3 may occur, along with the high QRS $_{2 \text{ and } 3}$, because of the position of the heart, even if it is normal in size. Similarly, we feel that an oblique heart, with marked, counterclockwise rotation around its long axis, irrespective of its size, may cause a downward T_1 in addition to the high QRS_1.

In other cases, the changes in the RS-T segment and the T wave may be due to the large area of the QRS complex, which is so often present in cases of ventricular hypertrophy. These suggestions, however, obviously do not cover all the possible mechanisms which can produce a downward T wave in the absence of myocardial damage. A more complete discussion of the above concepts, impossible in this paper, will be presented elsewhere.[23]

THE VALUE OF ROENTGENOLOGIC EXAMINATION OF THE HEART

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ROENTGENOLOGIC examination of the heart provides data regarding size, shape, and pulsation, as well as relationship to adjacent structures. The present report proposes to review critically the significance in the clinical diagnosis of cardiac disease of data obtained by conventional roentgenologic examination.

In order to make a diagnosis, it is essential to know the size of the heart. It is estimated with much greater accuracy roentgenologically than by percussion or palpation. In so-called normal persons, a fairly uniform correlation is found between the area of the posteroanterior projection and the height and weight.[1] Although a heart that is judged to be enlarged from "prediction" tables must be considered as likely to be diseased, a variation from the average can be anticipated regularly in normal subjects, so that deviations must be evaluated in terms of other clinical data. It must be borne in mind constantly that normality as a statistical concept refers only to average values. Furthermore, significant disease may exist in spite of so-called normal measurements. Indeed, the range about the average values is sufficiently large and the influence of the position of the diaphragm is of such importance that, in experienced hands, precise measurements are an unnecessary refinement, and may be reserved for actuarial or experimental purposes. Usually the experienced observer can compare the size of the heart to body habitus with sufficient accuracy by inspecting the teleoroentgenogram or the orthodiagram. Many observers are satisfied with simple fluoroscopic examination, although this requires greater discrimination.

The shape of the heart does not lend itself easily to classification. Although the terms "mitral configuration" and "aortic configuration" are still used, they have a place only when no diagnostic connotation is implied. More precision in the description of shape is obtained by considering the separate segments of the cardiac contour. Ordinarily, in the posteroanterior projection, for example, it is possible to identify five landmarks. On the right side the cardiac border joins above with the supracardiac segment and below with the diaphragm. On the left side the points are not as sharply defined. Below, there is a rounded nose just above or below the outline of the diaphragm which is described as the roentgenographic apex of the heart. More cephalad is a point on

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either side of which the pulsations are opposite: when the contour below contracts, the one above distends. The two segments may be immediately adjacent or may be separated from each other by a segment which pulsates less vigorously or appears still. In most cases these dividing points do not represent constant anatomic landmarks on the cardiac chambers. Comparison with post-mortem material and particularly with the angiocardiographic appearance shows clearly that they are more or less accidental points, where the projected chambers overlap. Hence, measurements made between these points cannot have any anatomic significance. This statement applies to the cardiac contour in all positions of the patient. Precision measurement of the individual chambers, therefore, cannot be attained, but experience does result in a certain visual dexterity in the examination of the contours between these points when correlated with body habitus, the position of the diaphragm, and the size of the heart as a whole. As an aid in the evaluation of these contours we shall present an analysis of the cardiac contour in the normal subject and in those diseases in which there is predominant enlargement of a single chamber. The analysis will be based largely upon angiocardiographic studies, confirmed, however, in most instances by post-mortem correlation.

NORMAL

In a normal person (Figs. 1*A*, 1*B*, 1*C*, and 1*D*), in the posteroanterior position, the right heart border is made up by the right auricle. At its junction with the supracardiac segment there is ordinarily some part of the ascending aorta. The aortic valve is situated at a variable distance within the shadow of the heart. The lower left contour is constituted by the left ventricle. The segment above this is made up by the pulmonary artery, the contour of which, however, usually is separated from the left ventricular contour by a short segment which does not opacify in the usual angiocardiogram, and most likely represents the left auricular appendage. The pulmonary valve also is hidden in the shadow of the heart. The pulmonary conus, which is the part of the right ventricle adjacent to the valve, does not form a part of the cardiac contour. In a few cases the descending branch of the left pulmonary artery may be projected so that its shadow merges with that of the pulmonary artery, and actually forms the contour of the middle left cardiac segment. As the subject is rotated into the right anterior oblique position, the pulmonary artery becomes the entire middle left arc. Only as the right lateral position is approached does the pulmonary conus also come into contour below the pulmonary artery. Since it is part of the right ventricle, its contraction is ventricular in phase, and is differentiated from the pulsation of the pulmonary artery above it, but not from the contraction of the left ventricle below it. In the left anterior oblique position the right ventricle may constitute part of the most caudad anterior contour in some cases. Angiocardiographic study suggests, however,

that most often the latter is obscured by the right auricular shadow. The lower left border in this position is made up by the left ventricle. There is no way to identify the boundaries of the right ventricle in this view. The so-called interventricular groove which is thought by some to be demonstrable in deep inspiration does not correspond to the position of the interventricular septum as seen angiocardiographically.[2]

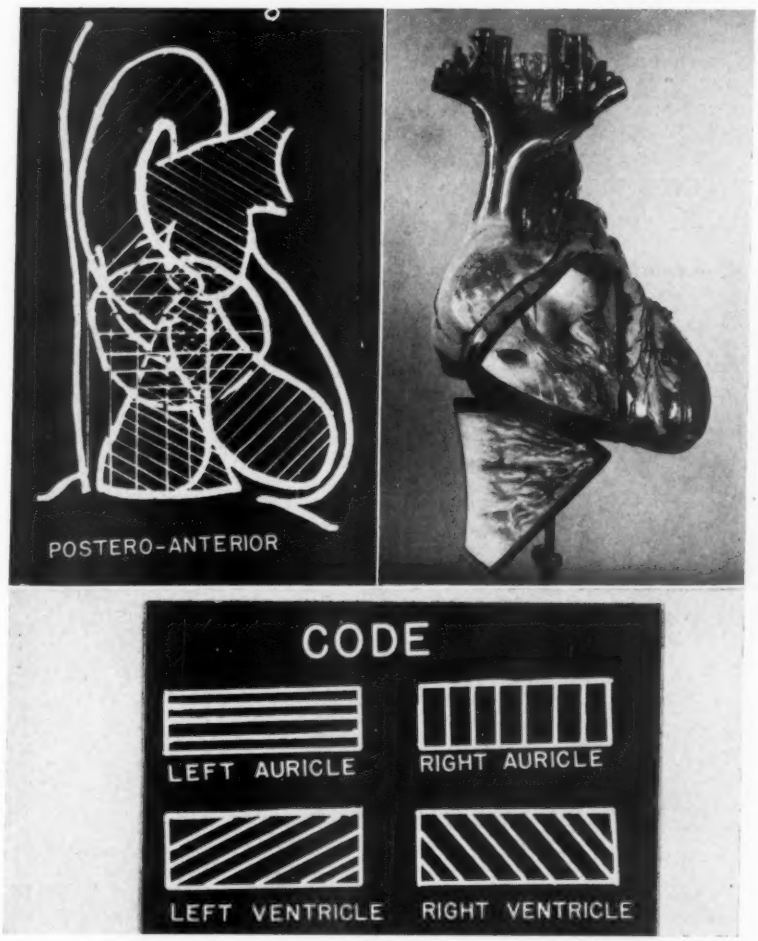

Fig. 14.—Analysis of the cardiac contours based upon angiocardiograms compared with a model of the heart rotated into a corresponding position. Posteroanterior view. (Right ventricle open.)

In the absence of calcification there is no way to establish the position of the cardiac valves, and any geometric patterns which may be traced through arbitrarily defined points have no anatomic counterparts.

PREDOMINANT ENLARGEMENT OF THE RIGHT VENTRICLE

The right ventricle is enlarged characteristically in cor pulmonale. Even in this condition, the case for study must be chosen carefully to

avoid a confusing left ventricular dilatation due to coronary sclerosis or hypertension. In the suitable case, when the right ventricle is the only chamber significantly enlarged, in the posteroanterior view the heart is found to be widened mainly to the left, and there is a prominence of the pulmonary artery segment of the middle left contour. The cardiac enlargement is seen also in the left oblique position, where, particularly, the portion of the heart merging with the shadow of the diaphragm is widened without protruding into the retrocardiac space. Analysis of the angiocardiograms shows that prominence of the pulmonary artery segment actually is due to dilatation of the pulmonary artery, which, in addition, is elevated above the usual position of this vessel.[3] Apparently, the elevation results from the fact that the right ventricle, which is dilated in all diameters, raises the artery above it. The artery also becomes tortuous, which tends further to exaggerate its convex contour.

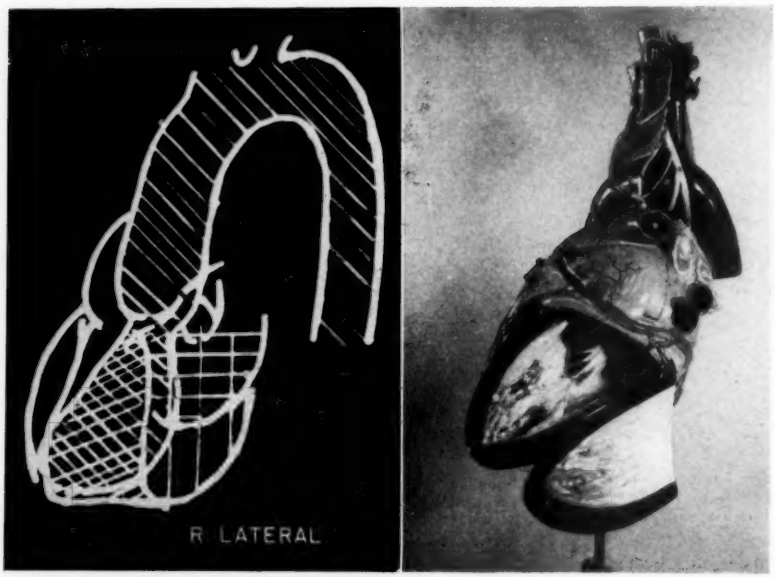

Fig. 1*B*.—Right lateral angiocardiogram. The model is turned into the left lateral position to show the left auricle. (Left ventricle open.)

The dilated right ventricle is hidden within the cardiac shadow in the posteroanterior and left oblique positions, and cannot be defined by any points on the contours. Only in the marked right oblique position does it form part of the contour in the pulmonary conus region. Then, as the patient is rotated into the lateral position, it occupies the entire anterior surface of the heart, obliterating the retrosternal space (Fig. 2). Enlargement of the heart to the right does not appear ordinarily until there is frank right-sided heart failure. It is demonstrable earliest in the left anterior oblique position, and apparently is associated uniformly with dilatation of both the right ventricle and the right auricle.

The same phenomena can be studied in connection with congenital pulmonic stenosis, which, for this purpose, need not be an isolated condition, for a complicating interventricular septal defect does not materially change the findings. In these conditions marked enlargement of the right ventricle is found anatomically. Roentgenologically the heart is enlarged to the left. There is no enlargement to the right,

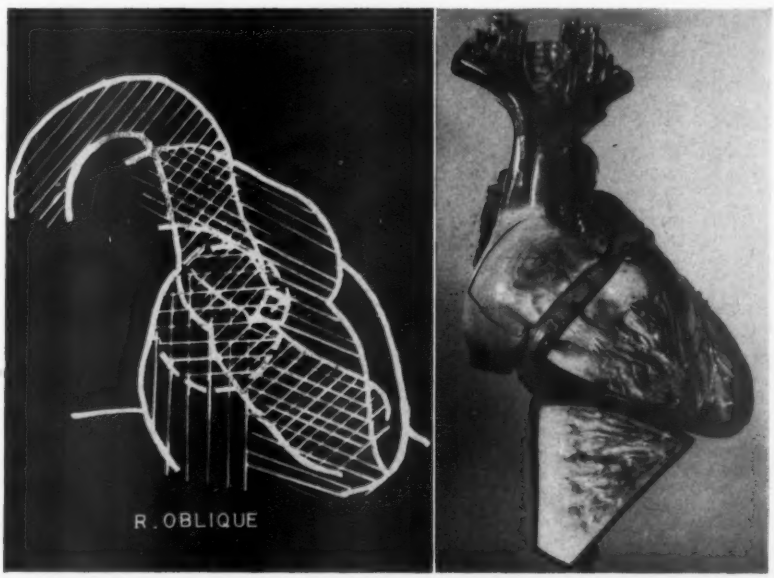

Fig. 1*C*.—Right anterior oblique position. (Right ventricle open.)

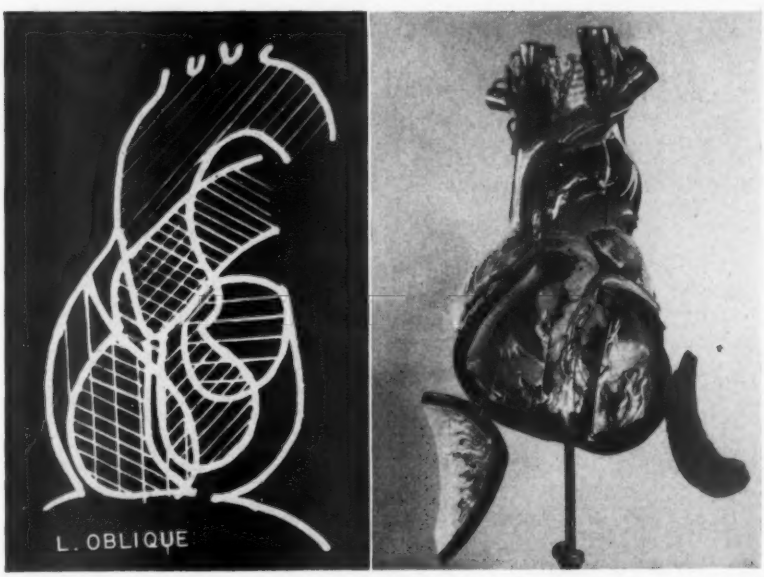

Fig. 1*D*.—Left anterior oblique position. (Both ventricles open.)

Fig. 2.—Posteroanterior and left lateral views in a case of cor pulmonale as the result of long-standing bronchiectasis. Right-sided heart failure was present for five years. Angiocardiograms and post-mortem examination revealed marked hypertrophy and dilatation of the right ventricle.

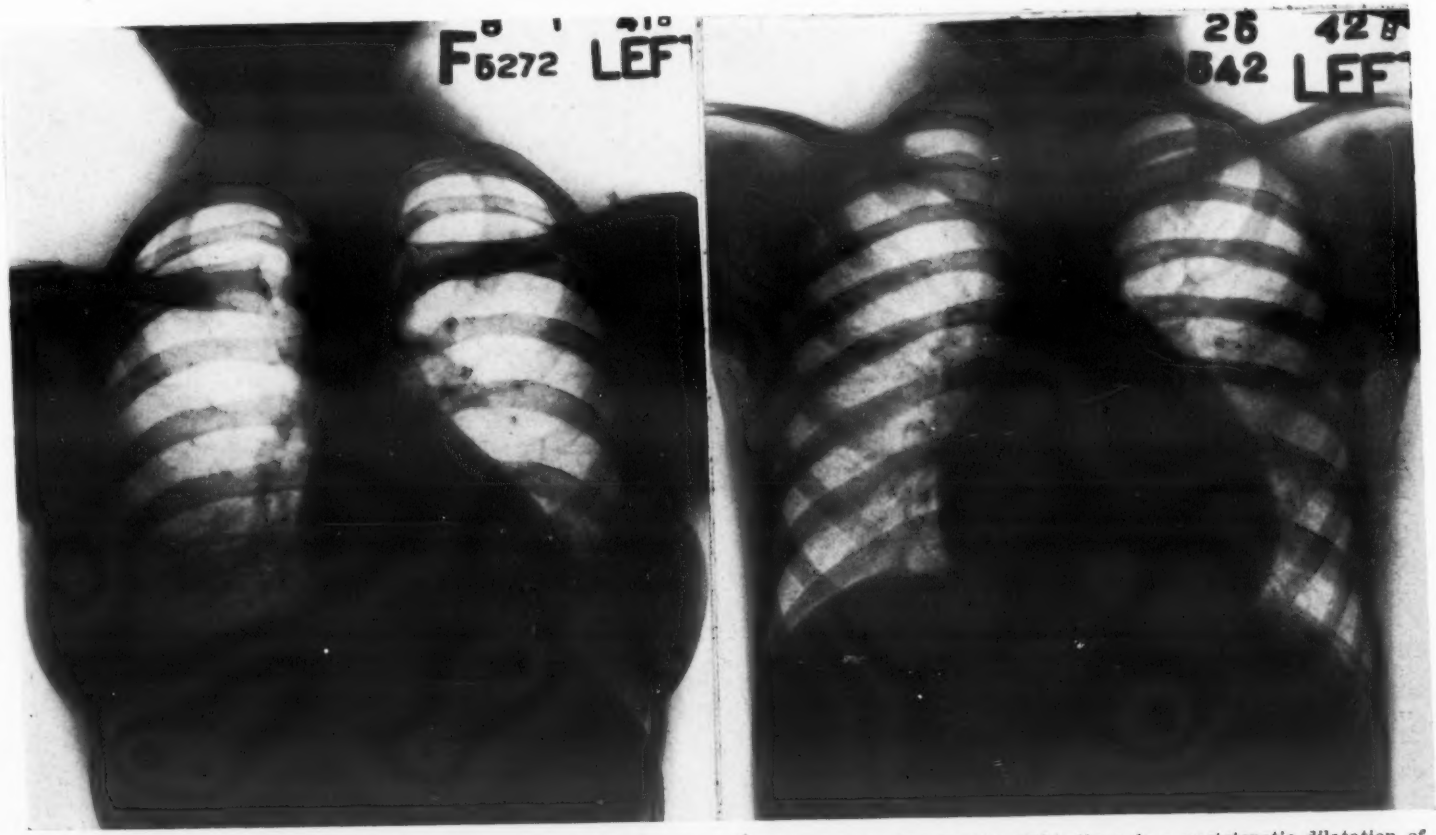

Fig. 3.—Cases of isolated pulmonic stenosis. On the left, the pulmonary artery is small. On the right, there is a poststenotic dilatation of the pulmonary artery. The convex "middle left curve" is due mainly to dilatation of this vessel.

either in the posteroanterior or in the left oblique positions. When the right, ventricular enlargement is mainly hypertrophy, as in the tetralogy of Fallot, the base of the heart just below the level of the pulmonary artery may not be significantly widened. If, however, there is also dilatation, as in isolated pulmonic stenosis, the base of the heart is widened. When, in addition, there is a poststenotic dilatation of the pulmonary artery, the middle left segment becomes very prominent, and the configuration cannot be differentiated roentgenologically from that of cor pulmonale as it is seen in emphysema or pulmonary fibrosis (Fig. 3).

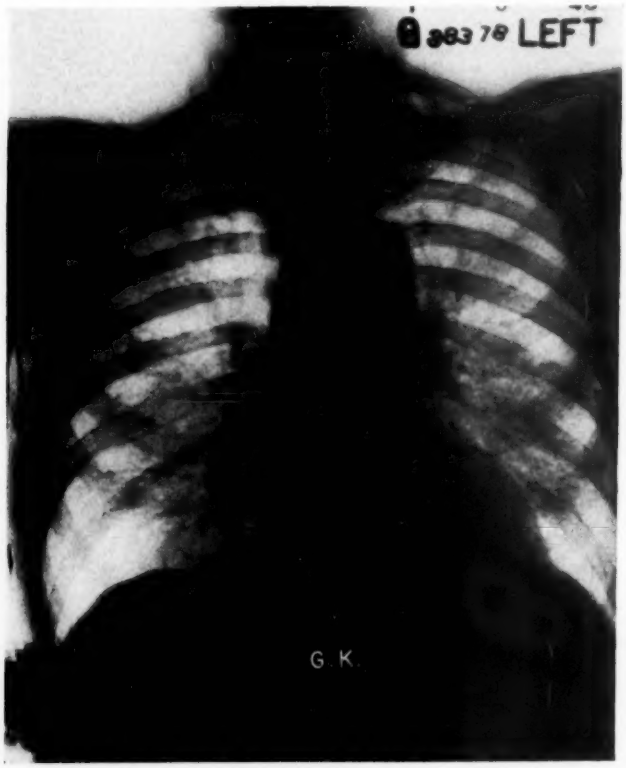

Fig. 4.—Cor pulmonale secondary to pulmonary fibrosis. Post-mortem examination revealed marked enlargement of the right ventricle. The left cardiac chambers were only slightly dilated and hypertrophied.

Since the right ventricle does not come into contour in any positions except the right anterior oblique and the right lateral, it follows that milder degrees of enlargement of this chamber will be demonstrated, if at all, only by displacement of adjacent chambers. For this reason, even moderate enlargement may be difficult to demonstrate and to differentiate from enlargement of the left ventricle. Occasionally, in the lateral view, obliteration of the retrosternal space will point to

right ventricular dilatation, in contrast to the large left ventricle, which intrudes into the retrocardiac space. The latter is demonstrated better in the left oblique view. Furthermore, in the posteroanterior view, widening of the heart just below the level of the pulmonary artery also may point to enlargement of the right ventricle. Neither of these criteria, however, is of great value when the dilatation is moderate and when the chest is barrel-shaped and emphysematous. To illustrate this conclusion we cite the fact that, in chronic emphysema, pathologically the right ventricle is found to be dilated in a high proportion of cases. Nevertheless, radiologically the heart often does not appear enlarged. Only when prominence of the pulmonary artery segment is taken as an indication of right ventricular enlargement, as Parkinson and Hoyle[4] suggested, is the incidence of right ventricular change as frequent as the anatomic data would lead one to expect. Fortunately, this criterion is generally valid because, in emphysema, the pulmonary artery is likely to be dilated when the right ventricle is enlarged. In the absence of pulmonary artery dilatation, the only indication of moderate right ventricular dilatation in emphysema is enlargement of the heart to the left, but this evidence is useless unless clinical data exclude dilatation of the left ventricle, and a pulmonary disease is present in which cor pulmonale might be expected (Fig. 4).

LEFT AURICULAR DILATATION

The outstanding example of predominant dilatation of the left auricle occurs in mitral stenosis. Roentgenologically it is characterized by a straightening or convexity of the middle left cardiac contour in the posteroanterior and right oblique positions. The chamber may be visualized as a dense area within the cardiac shadow; sometimes it projects to the right, and overlaps the right auricular contour. The left main bronchus is elevated, but this is seen better in the left oblique position. In the right oblique and right lateral positions the retrocardiac space is encroached upon. The esophagus is displaced posteriorly, as well as to the right, and is compressed. Angiocardiograms show that the pulmonary artery is elongated, elevated, and bowed anteriorly.[5] It is not ordinarily dilated to any marked degree. The right ventricle also is bowed anteriorly. Except when the left auricle is seen directly, the most accurate criterion of its size is the position of the esophagus. This must be observed critically, however. The impression made on the anterior surface of the esophagus by a predominantly enlarged left auricle is ordinarily sharply localized. It begins immediately below the level of the left bronchus and ends well above the diaphragm.

The right ventricle remains only moderately enlarged in mitral disease until advanced failure supervenes. Since the left auricle displaces

the right ventricle anteriorly, the size of the ventricle cannot be ascertained accurately roentgenologically. Occasionally it may be possible to judge the extent to which it contributes to the heart shadow by subtracting the contribution of the left auricle, visualized as a dense shadow, or suggested by the positions of the esophagus and of the left main bronchus. It may be assumed, also, that the larger the left auricle, the more likely it is that the right ventricle is dilated and hypertrophied. Enlargement of the heart to the right and anteriorly, judged from the left oblique position, often results entirely from displacement of the right chambers by a huge left auricle, rather than by enlargement of the right auricle and right ventricle, as is assumed ordinarily. In the same way, the left ventricle may appear large as the result of displacement, although generally this does not happen to the same extent as with the right chambers.

LEFT VENTRICULAR ENLARGEMENT

Left ventricular enlargement may take the form of concentric hypertrophy, with little or no dilatation (usually associated with hypertension), or eccentric hypertrophy with dilatation. The roentgenologic diagnosis of concentric hypertrophy is made with difficulty. Until there is significant increase in the volume of the heart, which does not occur with concentric hypertrophy alone, the roentgenologic diagnosis must be based upon the shape of the left ventricular contour. This becomes rounded as it is seen in the posteroanterior view, or somewhat better in the left anterior oblique position. However, the degree of "rounding" of a curve is difficult to define for practical purposes, and, considered critically, the observation is of limited value. It is fortunate that enlargement due to mild hypertrophy in hypertension is of no great significance clinically in so far as the cardiac status is concerned. A progressive increase in the size of the left ventricle in hypertension is accompanied by widening to the left and increase in length, and generally can be attributed to an associated aortic insufficiency or to coronary insufficiency. When hypertrophy is marked, so that cardiac volume increases, enlargement is easily detectable by correlating the usual measurements with habitus. The ventricle becomes elongated as well as rounded, and the apex cannot be separated from the gastric air bubble in deep inspiration (Fig. 5).

Concentric hypertrophy with dilatation is manifested first by an increase in the size of the ventricle, particularly in its long diameter. The increase in length is accompanied roentgenologically by enlargement to the left and posteriorly. In order to demonstrate this by measurement, it has been suggested that the length of the heart as a whole (L) be compared with the transverse diameter (T). A long diameter, more than 10 per cent longer than the transverse diameter,

is used to indicate enlargement of the left ventricle. Careful measurements by us, however, failed to confirm the value of this observation, which is not surprising when the definition of the long diameter of the heart is considered. The right cardiac-supracardiac junction has no constant relationship whatsoever to the position of the aortic valve; the latter is deep in the shadow of the heart, and its location is unpredictable unless it is calcified. Hence, the long diameter is not a measurement of the length of the left ventricle. Furthermore, a complicating feature is the fact that the long diameter is not mathematically independent of the transverse diameter. Therefore, until

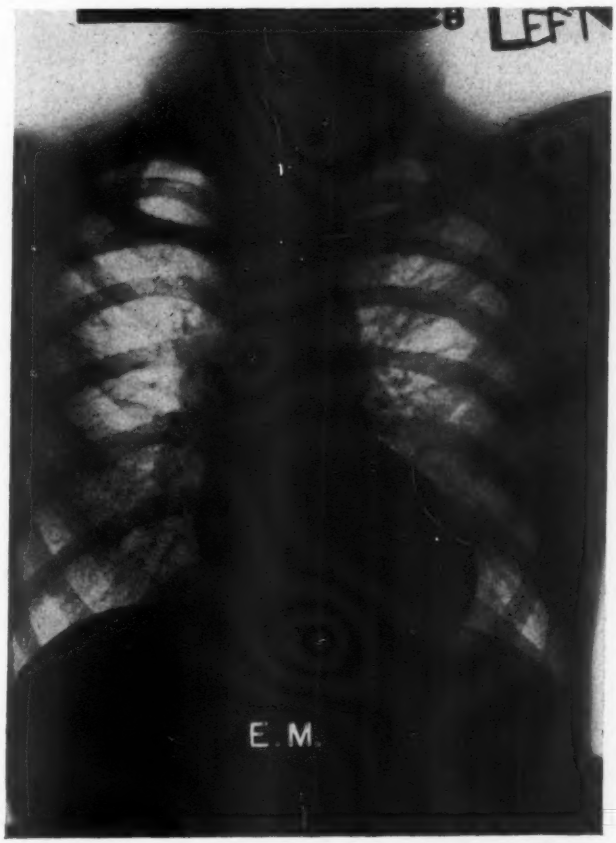

Fig. 5.—Marked hypertension in a case of coarctation of the aorta. The patient was asymptomatic.

the increased volume is detectable by measurement of the area of the whole heart, it is necessary to rely upon visual impression to ascertain whether the shape of the left ventricular contour is abnormal and whether it intrudes into the gastric air bubble excessively. Further left ventricular enlargement is manifested by widening to the left and posteriorly.

DISCUSSION

In view of the above data, it is well to reconsider what information is made available by cardiac roentgenology. The examination should provide fairly accurate answers to the following questions:

1. Is the heart enlarged? If so, is the enlargement mainly to the left, or is the right side also widened? Is it enlarged at the base just below the level of the pulmonary artery?
2. Is the shape of the heart abnormal when the patient is turned through various positions?
3. Is the left auricle enlarged?
4. Is the pulmonary artery dilated?
5. Are pulsations abnormal in any segments? (Discussion will be limited to myocardial infarction.)

From these data alone certain conclusions can be drawn. Predominant enlargement of the left auricle ordinarily indicates the presence of a mitral lesion, which may or may not be associated with other abnormalities. There are very few exceptions. For example, the chamber may be enlarged when the ductus arteriosus is patent and there is no mitral disease.[6] On the other hand, when it is enlarged in conjunction with an atrial septal defect, the mitral valve also is likely to be deformed. It is important to recognize certain variations in the position of the esophagus which simulate pressure by the left auricle alone. For example, the generally dilated heart will displace the esophagus posteriorly as a whole. In an occasional normal person there may be a gentle posterior bowing. In older persons the esophagus may be adherent to the descending aorta and therefore be displaced posteriorly; however, in this event, in the left oblique position it is seen to be separate from the heart and adjacent to the aorta. These conditions may be differentiated from the predominantly enlarged left auricle by the sharply localized pressure of the latter. On the other hand, it must be emphasized that lack of demonstrable enlargement does not exclude mitral disease. There may be no demonstrable left auricular enlargement with an early or functionally insignificant lesion.

The conditions without left auricular enlargement may be discussed in connection with whether or not pulmonary artery dilatation is present. Ordinarily, when the pulmonary artery is dilated the right ventricle also is enlarged. Exceptions are few. In cases of patency of the ductus arteriosus, in 50 per cent of which there is dilatation of the artery, it is the left ventricle, rather than the right, which is enlarged.[7] With idiopathic pulmonary artery dilatation there may be no significant chamber enlargement.[8] The prominent pulmonary artery segment which is seen in some normal adolescents and in Graves' disease may present a roentgenologic problem because it might be thought to indicate a mitral or a congenital lesion. As far as mitral disease is concerned, a predominant pulmonary artery segment is due

to left auricular enlargement, which is, therefore, the more important consideration. Differentiation from a congenital lesion is a clinical rather than a roentgenologic problem.

As far as left ventricular enlargement is concerned, in general, when the heart muscle is not impaired and when dilatation is due to an increase in the stroke output, the ventricle is lengthened in proportion to its width. This abnormality often represents a physiologic reaction, and is reversible when the increased stroke output returns to normal. On the other hand, myocardial damage with left ventricular dilatation is associated with widening of the cardiac shadow to the left and a transverse position of the axis of the heart. Indeed, in the absence

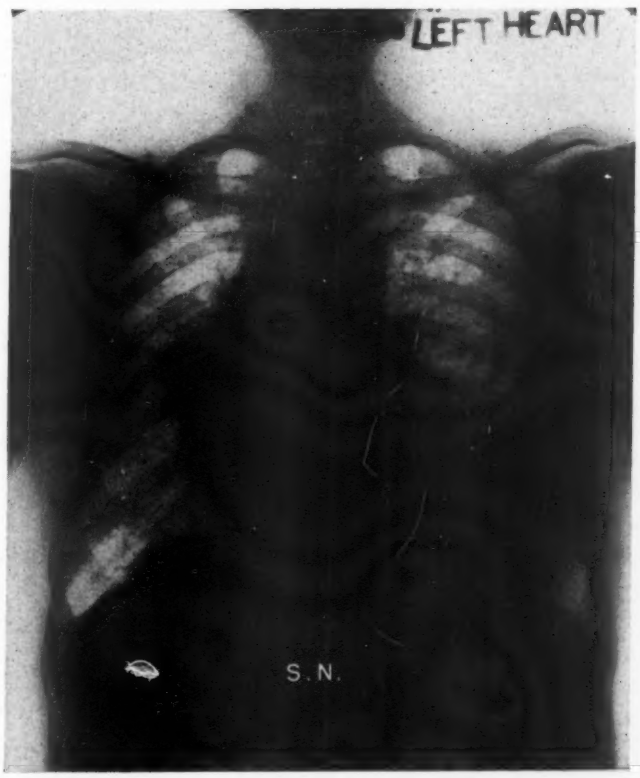

Fig. 6.—Left ventricular aneurysm due to coronary occlusion, associated with a huge left ventricle. The patient suffers only mild dyspnea and fatigue. Aside from two attacks of fresh coronary occlusion, there has been no change in the symptoms during the past fifteen years.

of aortic insufficiency this configuration usually can be attributed to myocardial disease. (The vitamin, mineral, and endocrine deficiencies are excluded from discussion.) It may be said, in general, that, in the clinical evaluation of a patient, it is extremely important to know the size and shape of the left ventricle, and the roentgenologic examination gives these data accurately. Percussion and palpation are not trustworthy. On the other hand, when the size of the left ventricle

is established, differential diagnosis is not aided greatly nor is any information made available in the individual case, from the roentgenologic observation alone, as to the functional capacity of the heart or prognosis (Fig. 6). This statement is not intended to minimize the importance of knowing the size of the left ventricle when it is considered in the light of the clinical diagnosis and other clinical data.

Fluoroscopic examination and, more accurately, the roentgenkymogram give information regarding the condition of the left ventricular muscle by observation of pulsation. There is no doubt that ordinarily this information is obtained more quickly and accurately from the clinical examination and the electrocardiogram. Occasionally, however, when these data are equivocal, an abnormal pulsation will be the only objective evidence of muscle damage, and, at least from the medicolegal point of view, may be very important when found. On the other hand, roentgenkymograms give no indication of functional capacity or of the possibility of future cardiac insults.[9]

CONCLUSION

It is generally realized at the present time that roentgenologic examination of an organ in most instances is only *part* of the clinical examination. This is true particularly of roentgenologic examination of the heart. The current criteria for the roentgenologic diagnosis of heart disease are based often upon physiologic reconstructions which do not occur as simply in practice. Certain important modifications have been suggested as the result of angiocardiographic study. There is no reason to use a method beyond its proper limits to extract information which is of questionable accuracy and which can be obtained more easily by other means. Hence, it is when the roentgenologic observations are considered critically as part of other clinical data that the examination is of real value. Alone, it may be insignificant or even misleading.

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OBSERVATIONS ON THE MECHANISM OF THE PHYSIOLOGIC THIRD HEART SOUND

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ALTHOUGH studies on the physiologic third heart sound have been carried on for many years, there has been no unanimity of opinion as to its cause. In 1907, Gibson[1] came upon the third heart sound in young athletes and in persons convalescing from infectious disease. He recognized the sound on auscultation after his attention had been drawn to it by waves interposed between the *v* and *a* waves in the jugular pulse. Gibson considered that the third heart sound may be caused by the floating shut of the auriculoventricular valves during rapid ventricular filling in early diastole. Almost at the same time, Hirschfelder[2] observed *h* waves in the venous pulse; he suggested that these waves might arise from the momentary diastolic shutting of the cuspid valves, which, in turn, might produce a third heart sound. However, he cautioned that there was no proof for this suggestion. Two years later, Thayer[3] concluded that the third heart sound was valvular in origin. Einthoven[4] studied the problem with a phonocardiograph. He considered the most likely cause of the third sound to be stretching and snapping of the closed semilunar valve membranes in early diastole.

In recent years, other observers have postulated that the third heart sound may be muscular in origin.[5-8] The suggestion was made that, in early diastole, the rapidly distending myocardium becomes suddenly taut, producing audible vibrations. Leonhardt[8] observed regular, sharp, outward movements of the ventricular wall of the dog heart which coincided with a third heart sound. Lewis and Dock,[9] however, studying the origin of heart sounds, concluded that any sound arising from the heart must be valvular in origin because the ventricular myocardium is too thick to permit sudden motions to produce audible vibrations. Recently, Boyer, Eckstein, and Wiggers[10] suggested that the third sound might arise from the impact of the heart against the chest wall. This idea was subsequently investigated by Boyer,[11] who was able to record the third heart sound from the exposed, beating dog heart; he felt that the sound arose from the cardiac wall.

In order to study further the mechanism of the physiologic third heart sound, the following experiments were performed.

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METHODS

Dogs were anesthetized with veterinary nembutal. In each experiment the thorax was opened to expose the heart, and an ordinary Starling heart-lung preparation was set up. The heart-lung preparation was used so that a slower ventricular rate and optimum blood pressure and cardiac output could be maintained for the production of clearly recognizable heart sounds.

The heart sounds were recorded directly from the left ventricular myocardium by means of a Wiggers-Dean capsule.[12] The capsule was connected by flexible rubber tubing, about 70 cm. long, to a small glass funnel (2 cm. in diameter) which was placed on the left ventricle immediately above the apex. The capsule membrane was prepared in the usual way;[12] a small mirror (1 mm. square) was applied to the membrane at one edge. Because of the intensity of the heart sounds when they are recorded directly from the heart, it was necessary to render the system less sensitive by placing the mirror as close to the edge of the capsule as possible. The membranes showed a natural frequency of 75 to 85 cycles per second, and were adequately sensitive for our purpose. A suitable optical system was utilized to reflect a light beam from the capsule mirror into an electrocardiographic photokymograph.

The recorded heart sounds were synchronized with electrocardiographic tracings in order to record the events of the cardiac cycle when the heart was beating empty. This was accomplished by embedding one electrode in the right shoulder muscles; the other electrode was inserted into the muscle of the diaphragm in the midline. The heart sounds and electrocardiograms were recorded on the same bromide paper strip.

It seemed desirable to eliminate the possibility that motion of the auriculoventricular valves may produce the third heart sound. Valve motion was prevented by means of special valve "splints." The "splints" were small discs, 1 cm. in diameter, to which rods were attached perpendicularly at the centers. The discs were then passed through small incisions in the right and left auricular appendages and were pushed into the ventricular cavities. When in place, the splints were so small that ventricular function was not hindered; with the heart beating empty, traction could be applied to the rods to hold the valves in a position of closure and to prevent any motion of the membranes. After each experiment the heart was incised and the position of the splints was verified.

During each manipulation of the experiments, careful auscultation was carried out on each heart in order to confirm sound elements noted in the curves.

RESULTS

The Third Heart Sound in the Normally Beating Heart.—When the bell of a stethoscope was placed on the left ventricle above the apex, a third heart sound was invariably heard in early diastole. This sound was distinct from the second heart sound. It seemed short and dull, with a quality of sound like a short *puff* or *pud*, and was less intense than either the first or second heart sounds. Sudden distention of the ventricles occurred simultaneously with the third sound, as nearly as one could judge by concomitant auscultation and inspection of the heart.

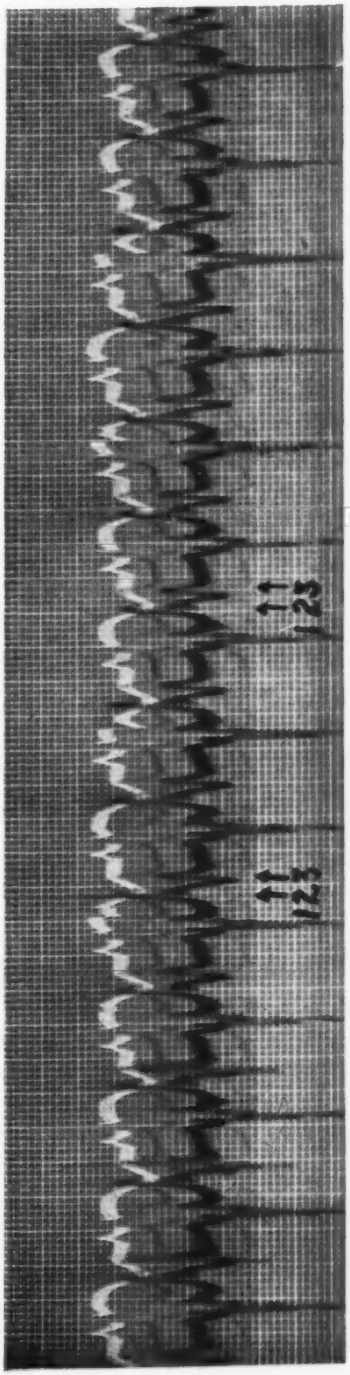

Fig. 1.—Heart sound tracing and electrocardiogram simultaneously recorded from the normally beating heart (heart-lung preparation). Sounds were recorded from the left ventricle just superior to the apex. The three heart sound deflections are clearly recognizable (marked *1*, *2*, and *3*). In this instance the third heart sound is represented by a diphasic, peaked deflection, occurring after the apex of the T wave.

Records of the heart sounds (also taken from the left ventricle just superior to the apex) showed the first sound as a group of large, peaked deflections followed by the finer deflections of the second sound (marked as *1* and *2* in Fig. 1). The first sound waves accompany and immediately follow the R wave of the electrocardiogram; the second sound occurs at the peak of, or on the descending limb of, the T wave. The deflection representing the third heart sound follows the second sound by approximately 0.08 to 0.15 second. In the records it usually appeared as a simple, peaked wave, inverted or upright, often preceded and followed by smaller spikes in opposite direction to the higher point. Occasionally the third sound wave was diphasic in contour. The amplitude of the wave was generally somewhat less than that of the second heart sound.

Considering all of these factors, it seemed probable that the deflection occurring in early diastole represented the physiologic third heart sound.

Effect on the Third Heart Sound of Preventing Venous Inflow and Splinting of the A-V Valves.—Studies with the valves immobilized and the heart beating empty were carried out on seven preparations. Continuous tracings were made throughout the procedure. When control records (and auscultation) had been made with the valve splints in the ventricular cavities and with the heart beating normally, the venous inflow into the heart was shut off. Tension was applied to the splints when the cardiac output had become nil. On auscultation, within a few beats after stopping the venous inflow, there was an abrupt diminution, then complete absence, of the second heart sound. The first sound remained clear, but seemed shorter and more dull. The third heart sound remained distinctly audible, although less intense; it persisted, along with the first sound, as long as myocardial contraction remained vigorous. With re-establishment of venous inflow and release of the cuspid valves; the second heart sound returned as blood pressure was restored; the first and third heart sounds became sharper and more intense.

Fig. 2 shows a continuous tracing of one of these experiments. In the control tracing (*A*) the first and second heart sound deflections are readily identified by their sharp, peaked profiles and by correlation with the electrocardiogram. The third heart sound is represented by a steeply inverted, pointed wave, following the second sound by about 0.1 second, and occurring just after the T wave. When venous inflow was stopped and the A-V valves splinted, the second heart sound was lost within a few beats (*B*). However, the third heart sound persisted, becoming shallower and less sharp (although audible). The finer serrations of the first heart sound disappeared, leaving the coarser waves. With the restoration of venous inflow and cessation of tension on the A-V valves, myocardial efficiency was quickly restored (*C* and *D*); the second heart sound waves returned, the third sound waves became deeper, and the entire curve resumed its "normal" shape.

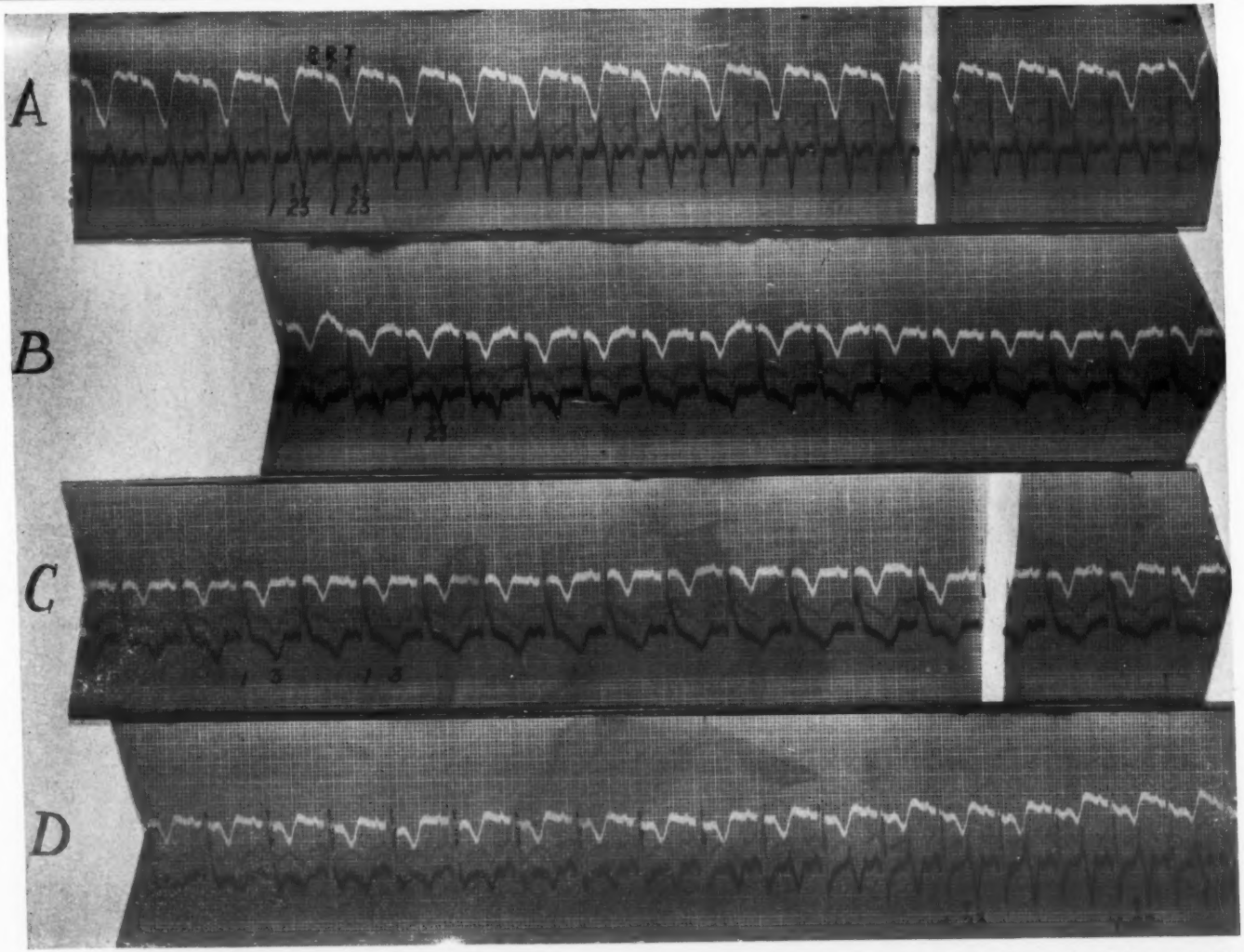

Fig. 2.—Continuous tracing of heart sounds and electrocardiogram during whole of an experiment. Curve *A*, of the normally beating heart, shows the three heart sounds clearly (marked). The vertical white mark in *A* is the point where venous inflow was cut off and "splints" placed on the A-V valves. In curve *B*, the second heart sound has gradually disappeared with the heart beating empty; the first and third heart sounds persist (curves *B* and *C*). Vertical white mark in *C* is point where venous inflow was re-established and the A-V valves released. Curve *D* shows gradual return of cardiac function; note reappearance and increasing amplitude of second heart sound. Changes noted in the heart sound tracing were confirmed by auscultation of the heart.

The Third Heart Sound in the Empty, Beating Heart Without Valve Immobilization.—In seven heart-lung preparations, venous inflow was stopped without splinting of the cuspid valves. In each experiment the first and third heart sound waves were found to persist while the heart was beating empty; the second sound disappeared with loss of blood pressure. The recorded tracings did not differ materially from those obtained from the empty beating heart with the valves immobilized. As with the former experiment, the first and third heart sounds could be heard during the period when there was no inflow into the heart.

DISCUSSION

The accurate identification of any "sound" arising from the heart will depend on (1) audibility, and (2) the graphic recording of the "sound" so that it may be studied with respect to other heart sounds and to the cardiac cycle. These conditions appear to have been fulfilled with regard to an early diastolic heart sound in the exposed, beating dog heart.

The third heart sound, on the tracings, always appeared in simpler contour than the first or second heart sound deflections (Fig. 1). Generally, a dominant upright or inverted, pointed wave occurred, often preceded and followed by smaller peaked deflections in opposite phase. When the heart beat empty, the third sound waves became of less amplitude (although retaining a pointed contour), and the smaller opposing waves were lost (Fig. 2). More important is the fact that a sound, in early diastole, was *audible* as long as the strength of myocardial contraction was maintained.

The persistence of the diastolic sound with the heart beating empty and with arrest of motion of the auriculoventricular valves introduces the possibility that the sound arises from the heart wall. Experimental evidence suggests that sounds from myocardial contraction may be recorded as simple waves with steep, sharply defined onsets. Smith, Gilson, and Kountz[13] studied the muscular element of the first heart sound by introducing balloons into the ventricular cavities and inflating the balloons to restrain all motion of the auriculoventricular valves. The sounds were recorded with a cathode-ray oscillograph. They found that a short, dull sound could be heard at the onset of systole, corresponding to the time of the first heart sound when the valves were thus immobilized. They further observed that a sharp, single decrement occurred in the oscillographic tracing synchronous with the sound. These observers postulated that the myocardial muscle fibers may represent, in a sense, a vast number of lax cables; when the muscle contracts, the lax fibers become suddenly taut in toto, producing audible vibrations.

Gilson[14] has recently observed the sharpness and dullness of clicks developed from simple electrical wave forms. He used a triode amplifying tube, so arranged that a telephone receiver was activated by the

plate current; upon opening a switch in the grid circuit, the plate current increased along a somewhat S-shaped time course; the rise at the foot of the curve was much more abrupt than was the approach to plateau level. The conclusion was reached that the click produced by the current change was represented by the upswing early in the curve. The sound was a click which had a sharper or duller quality according to whether the onset of electrical change was more sudden or more gradual. From these observations, it seems quite probable that the dull or sharp quality of a heart sound, such as the third sound as recorded in these experiments, may be due to relatively simple impact phenomena; other vibrations may be superimposed on these to modify the general quality of the heart sound. It also offers clarity to the fact that the rather simple wave forms which occur at the onset of systole and in early diastole, with valvular elements eliminated, have definite acoustic properties.

With this experimental evidence at hand, it appears that the third heart sound, at least in part, arises from the heart wall. Furthermore, since the third sound occurs at the time of rapid ventricular filling, it is possible that abrupt stretching of the myocardium produces the sound, as was suggested by earlier investigators.[5-8]

Boyer[11] was able to record third sounds directly from the myocardium by using a small, shallow bell placed on the heart. In addition, he found that a sound, identical with the third heart sound, occurred when the heart was allowed to strike the receiving bell gently. The force necessary to produce this sound was extremely small. Since third heart sounds were also noted when the heart was placed in a glass cardiometer, where no impacts were possible, he concluded that the phenomenon arose from the heart wall. Our conclusions are in essential agreement with his. On the other hand, Dock[15] and Lewis and Dock[9] have contended that the myocardium is so thick that its movements do not produce sounds. They state that motion of the valves is the only possible source of sound from the heart. Although valvular elements contribute largely to the first sound, and probably entirely to the second sound,[13] this does not appear to be true of the early diastolic third heart sound recorded from the dog heart. Dock's contention, therefore, is not supported by the observations of Boyer[11] nor by the experiments reported here. Indeed, it seems definite that any motion of the heart, whether valvular or muscular, may produce a sound, provided the motion is of sufficient strength and abruptness of onset.

These experiments emphasize again the presence of elements initiated by the heart wall in the first heart sound. The *first*, as well as the third, sound was noted in the procedures involving restraint of the cuspid valve leaflets, and the resulting first sound wave became nearly as simple as the deflection of the third heart sound.

SUMMARY

An early diastolic third heart sound was heard on direct auscultation of the left ventricle of the heart-lung preparation. Tracings of the heart sounds, using a Wiggers-Dean capsule, showed a deflection early in diastole which was apparently synchronous with the sound.

When blood flow into the heart was cut off, so that the heart beat empty, and motion of the cuspid valves was eliminated by splinting of the leaflets, the first and third sounds persisted.

It was concluded, therefore, that the third heart sound, as recorded from the normally beating dog heart, may arise from the heart wall. The observations further indicated that a mechanical disturbance of apparently simple wave form may have acoustic value, and that the third heart sound is often of this form.

The author wishes to express his gratitude to Dr. Arthur S. Gilson, Jr., Department of Physiology, for his assistance in this work.

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Clinical Reports

CLINICAL ARREST OF ENDOCARDITIS LENTA BY PENICILLIN

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FLOREY and Florey[1] reported the use of penicillin in the treatment of one patient (Case 15) with endocarditis due to *Streptococcus viridans*. The penicillin was administered at intervals of one to three hours for thirty days (total dose, 4,670,000 units). During this time there was marked improvement. After the penicillin was discontinued, the temperature mounted to its original height in a week, appetite was lost, and the blood culture again became positive at the end of three weeks. The patient died after another three weeks. The streptococcus apparently developed a considerable resistance to the penicillin.

Keefer and his committee[2] reported disappointing results in the treatment of endocarditis with penicillin. Loewe and his associates,[3] on the other hand, have reported a series of unbroken successes in the treatment of bacterial endocarditis with penicillin and heparin, and, more recently,[4] have reported observations on a larger number of patients with only a few failures.

During many years of continued study of endocarditis, we have observed very few survivals. In our series there have been two examples of recovery from clinically evident staphylococcic endocarditis and three recoveries from meningococcic endocarditis; all five patients were well at the last report, two to six years after apparent cure. In all five the diagnosis was based on clinical signs and persistently positive blood cultures. Until 1943, we had not observed a single instance of genuine arrest of endocarditis due to *Streptococcus salivarius*, which is evidently the commonest form of so-called subacute bacterial endocarditis. At present we have under observation several patients in this category in whom the course of the disease has been favorably influenced by the use of penicillin. A detailed report of one example of apparent arrest of the disease would seem to be of scientific as well as of general human interest, particularly because the successful treatment in this case followed a long period of deterioration which was thought to have attained the terminal stage.

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Presented in part before the New York Heart Association, New York, Feb. 1, 1944.

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From the Department of Bacteriology and the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

CASE REPORT

M. F., aged 32 years, a graduate nurse and the wife of a physician, previously healthy and without signs of cardiac defect, had an inflamed tooth extracted, in the usual sitting position, on Feb. 22, 1943. After this there was a persistent fever; this was at first ascribed to osteomyelitis of the jaw, but, after the development of a mitral murmur and the recovery of bacteria from the blood, it was recognized as the fever of bacterial endocarditis. The patient was admitted to the New York Post-Graduate Hospital on April 30, 1943, with the diagnosis already established. The most important subsequent observations are indicated on the graphic charts.

The period from April 30 to May 31 shows the sort of record that is commonly observed when a sulfonamide is administered. The systolic murmur, the positive blood culture on April 30, the petechia in the finger on May 1, and the accelerated erythrocyte sedimentation rate on May 3, along with elevated temperature and pulse rate, present a characteristic picture. Sulfadiazine, in a dose of 6 Gm. per day, with strict rest in bed, brought about some amelioration, but the bacteria persisted in the blood stream (12 per milliliter on May 17, and 18 per milliliter on May 24). The abnormal sedimentation rate remained evident and a new embolic spot appeared on May 16. On May 17 the administration of thiobismol, in a dose of 15 mg. twice daily by intravenous injection, was initiated, and, on May 19, intravenous injections of small amounts of citrated blood[5] were begun. The detail of these treatments may be followed in the charts.

In the next thirty-two days, from June 1 to July 2, there was more evidence of deterioration. Embolism to the brain on June 1 and the development of dysuria on June 6 caused us to discontinue the sulfadiazine. An antivirus filtrate, prepared by filtering an old autolyzed culture of the specific streptococcus, was given by daily intravenous injection from June 5. Neoarsphenamine in small doses was substituted for the thiobismol from June 9 to 12. The temperature attained a higher level; many conjunctival petechiae appeared; there was blurred vision and, on June 14, a hemorrhagic spot appeared in the right ocular fundus; the blood pressure fell, and emaciation rapidly progressed. The blood culture of June 14 developed 90 colonies per milliliter of blood. Chills and vomiting added to the distress of the patient. She received the last rites of the Church on June 18. In desperation, the sulfadiazine was started again on June 22, but was quickly discontinued. A limited quantity of partially processed penicillin became available on June 23, and this was found to exert a very powerful bacteriostatic effect in vitro upon the streptococcus of this patient. It was therefore administered by intramuscular injection in small doses, estimated as 100 to 200 Oxford units, every three hours. The supply of blood for transfusion failed on June 28, and intravenous injections of an iron preparation were given. On July 1 bilateral retinal emboli occurred, resulting in serious impairment of vision.

In the thirty-two days from July 3 to August 3 there were progressive loss of weight, mental confusion, a definite cerebral insult on July 21, splenic infarction on July 31, and slight hematuria on August 3. The available penicillin was sufficient for only small doses. The daily small transfusions doubtless helped to prolong life. The temperature tended to a lower level after July 25, and one gained the impression

that the slightly larger doses of penicillin might be contributing something of value.

From August 4 to 15 there was distinct improvement, and every effort was made to obtain increased supplies of penicillin for the patient, but without success. It was necessary to reduce the dose to approximately 100 units every three hours on August 15. The temperature rose and a

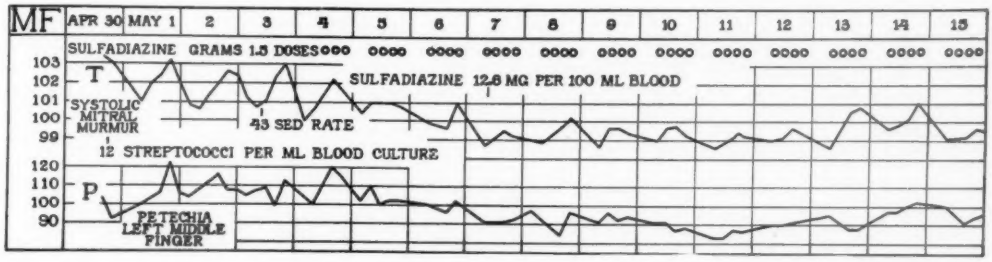
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Fig. 1.

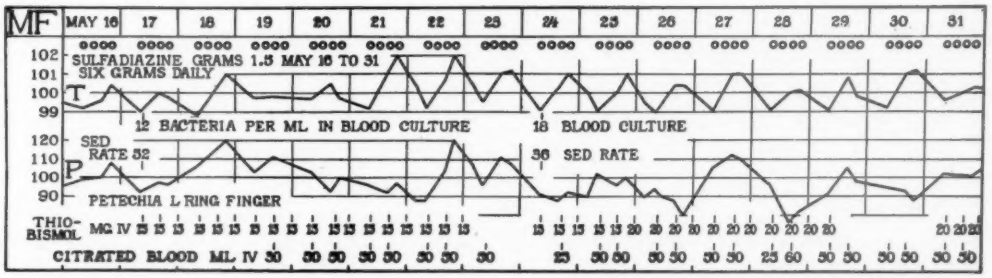
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Fig. 2.

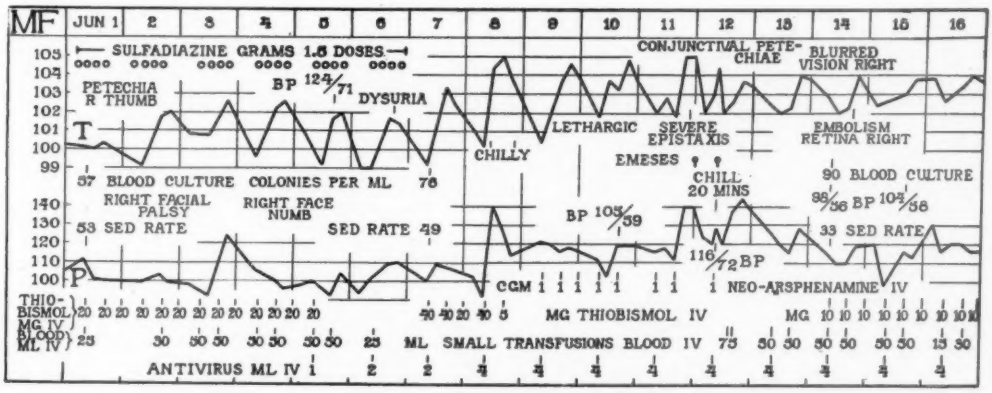

Fig. 3.

severe infarction of the spleen on August 17 caused us to omit the transfusions for a time. By the last of August the end seemed near. Inability to take or to retain food, physical exhaustion, and emaciation were extreme. At this time, however, we received word of encouragement in regard to supplies of penicillin, but the immediate change in the situation resulted in complete lack of this drug from September 4 to 9.

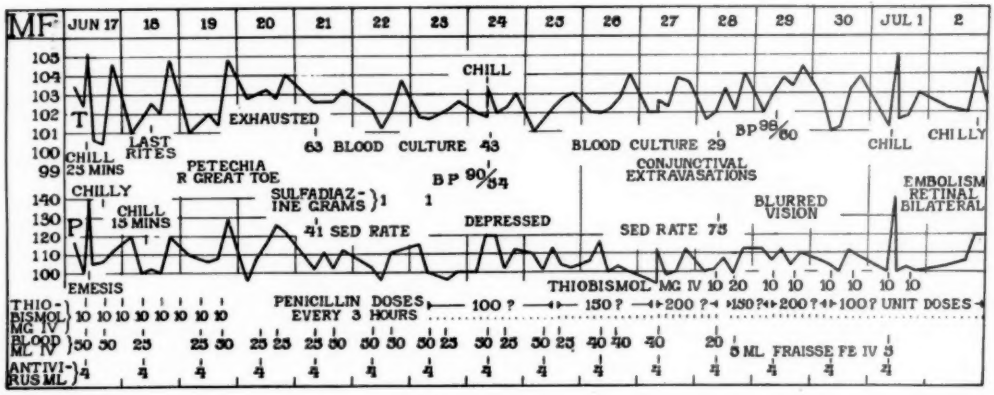
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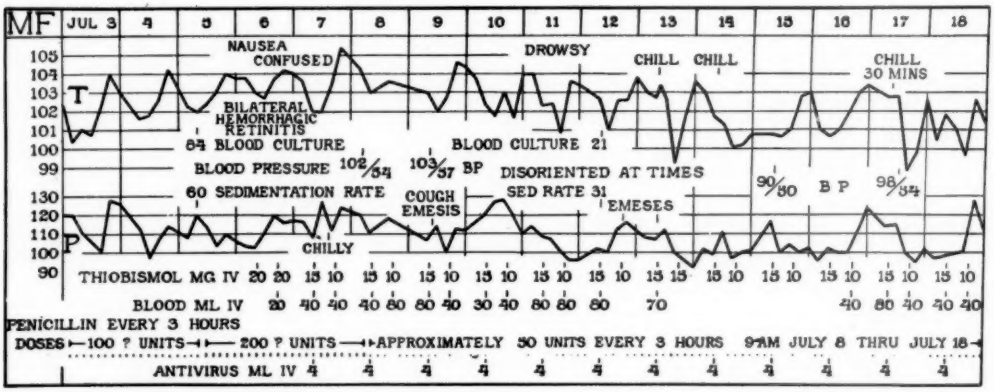
Fig. 4.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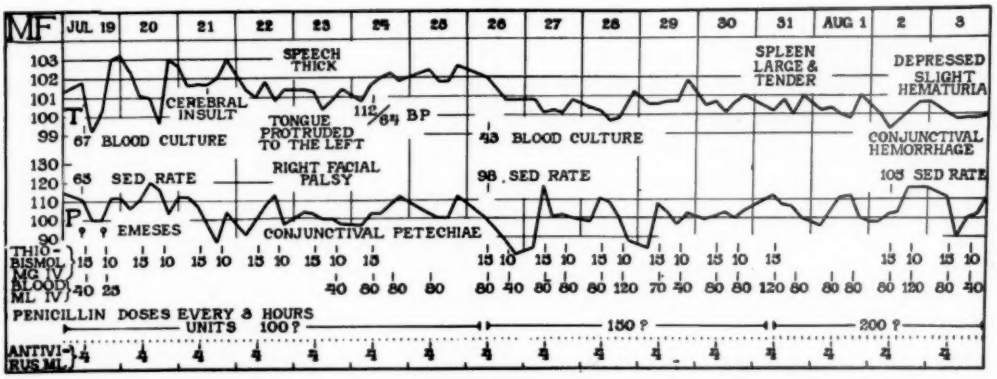
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RIGHT FACIAL PALSY
65 SED RATE
? ? EMESES
CONJUNCTIVAL PETECHIAE
43 BLOOD CULTURE
98 SED RATE
SPLEEN LARGE & TENDER
DEPRESSED SLIGHT HEMATURIA
CONJUNCTIVAL HEMORRHAGE
105 SED RATE
THIOBISMOL MG IV 15 10 15 10 15 10 15 10 15 10 15 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10 15 10
BLOOD ML IV 40 25 40 80 80 80 80 40 80 80 80 120 70 40 80 80 120 80 80 80 120 80 40
PENICILLIN DOSES EVERY 3 HOURS UNITS 100 ? 150 ? 200 ?
ANTIVIRUS ML 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4

Fig. 6.

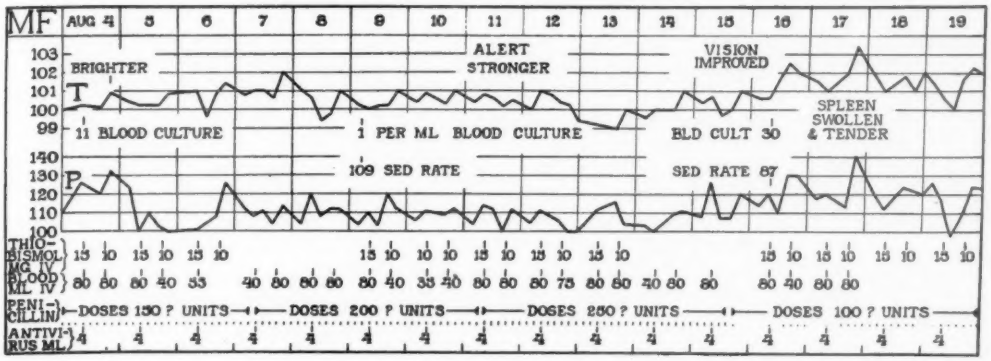

Fig. 7.

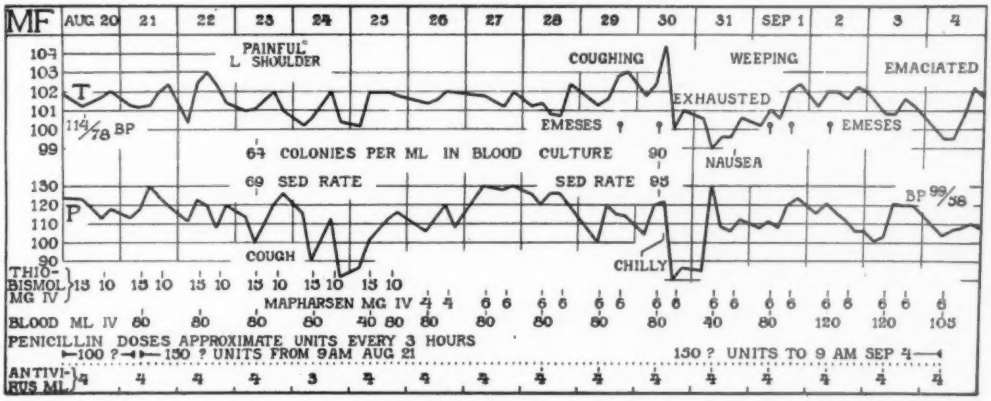

Fig. 8.

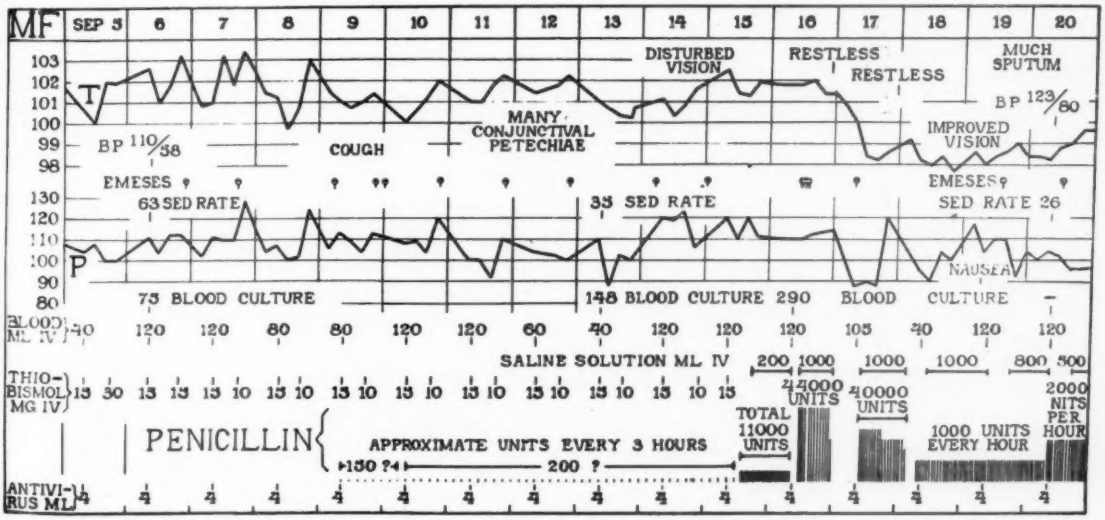

Fig. 9.

The period from September 5 to October 6 included the turning point from utter despair to encouraged optimism. The period of total lack of penicillin was terminated on September 9 by the miraculous renewal of the former meager supply, which was, however, inadequate to halt the progress of deterioration. The blood culture on September 6 developed 75 colonies per milliliter of the patient's blood, that taken on September 13 developed 148 colonies, and one taken on September 16 developed 290 colonies per milliliter. However, on September 15, a dramatic release of the supply of penicillin permitted the administration of 11,000 units from an icejacket container by intravenous drip from 2:30 P.M., September 15, to 8:30 A.M. on September 16. This was followed by 44,000 units from noon to midnight. Then there was an interruption due to technical trouble with the drip. This was started again at 10:30 A.M. on September 17, and continued with some irregularity until 4:00 A.M., September 18, when a total of 40,000 units in 1,000 ml. of saline had been given. Again there was an interruption. However, at 8:15 A.M. on September 18, the administration was systematically arranged so that the penicillin could be given every hour by direct intravenous injection during the day and by injection into the rubber tube of the saline infusion during the night without interruption. This program was followed until September 27, with an increase of penicillin to 3,000 units per hour for a short time on September 25, and then 2,500 units per hour to September 27. This technical method would appear to be most economical with respect to the expenditure of penicillin, but it required almost constant attention. Furthermore, the continuous infusion at night was resented by the patient as she became more alert. On September 27, the technique was revised so that the penicillin was given every two hours, by direct intravenous injection when convenient and by intramuscular injection at other times, ordinarily at night. Interruption of sleep at night proved not to be very serious for the patient.

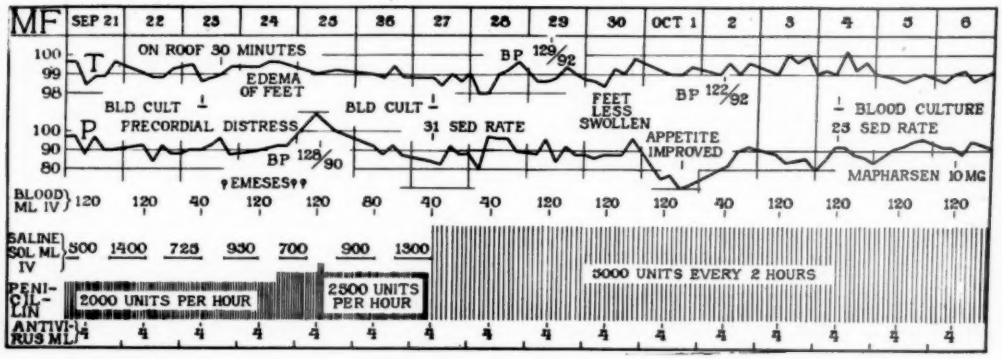

Fig. 10.

The response was very dramatic. The fever declined on September 17, and the blood culture taken on September 20 remained sterile, as did all subsequent blood cultures. There was evidence of pulmonary congestion and possibly pneumonia, with abundant sputum, on September 19 and 20. The blood pressure rose to 123/80 on September 20.

The period from October 7 to November 7 was one of slow convalescence, with gradual increase in weight and return to normal of the sedimentation rate. On October 18, the penicillin program was changed

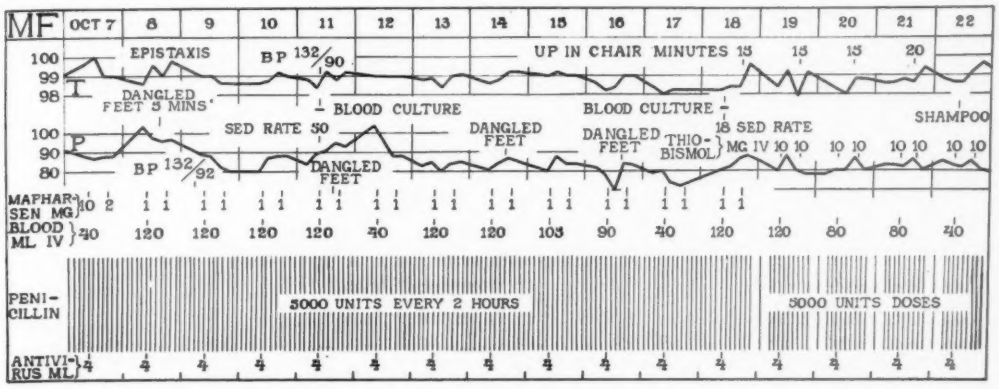

Fig. 11.

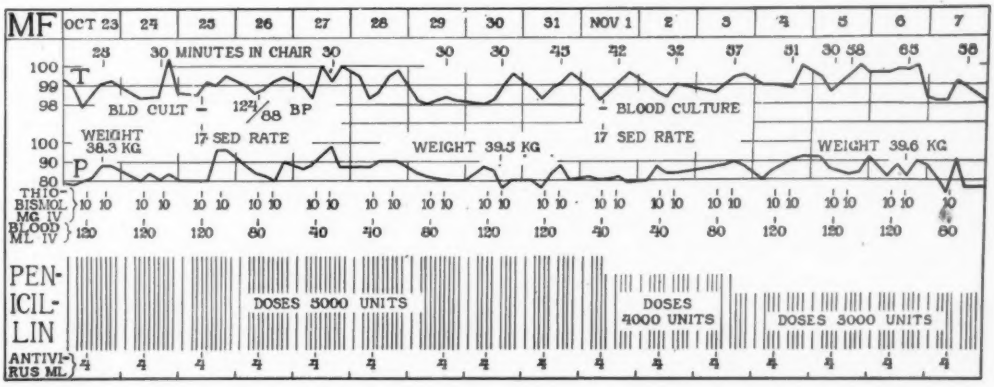

Fig. 12.

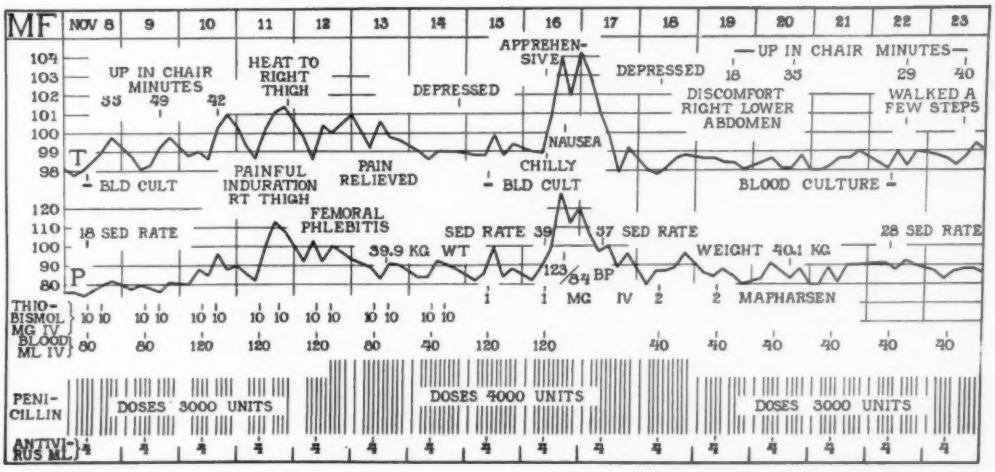

Fig. 13.

to allow intervals of four hours between doses at night, and, on October 30, the dose previously given at 1:30 P.M. was also discontinued. This saved annoyance to the patient and effort of the clinical staff, but was probably not a makeshift to be recommended.

From November 8 to December 9 was a period of uncertainty as to the best procedure. Success seemed assured if only we could continue on the proper course. The patient was eating well and gaining weight and strength, but was still very weak. Apparently she strained her right thigh on November 10 while getting back into bed, and femoral phlebitis was recognized on November 12. Activity was at once restricted and the dosage of penicillin increased. On November 16 there was a sharp rise in temperature, associated with chilly sensations and nausea. Pulmonary embolism was suspected, but this suspicion was not confirmed by physical examination. The sedimentation rate was disturbed at this time; it was 39 mm. per hour on November 16, and 57 mm. per hour on November 18. The spleen, which had been easily palpated for several months, still remained hard and extended 3 cm. below the costal margin on November 19. It was no longer sensitive to palpation. Improvement was quickly re-established, and, after November 26, the patient was up and about daily. There was a remarkable increase in her appetite, and the effect of this was reflected in the increased weight.

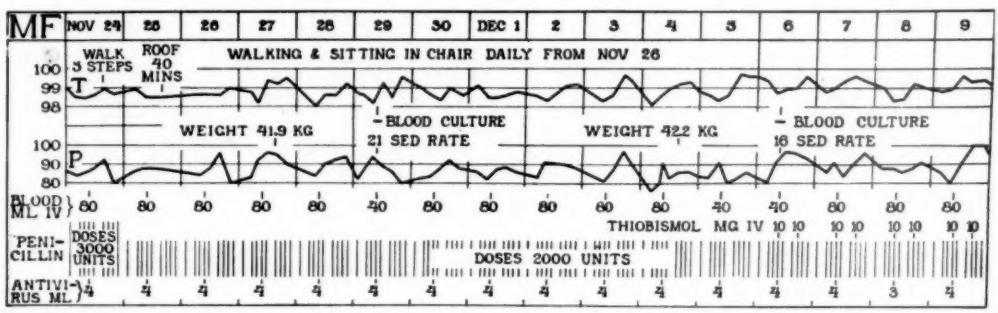

Fig. 14.

In the period from December 10 to January 10 there was first the psychological problem of keeping the patient in the hospital, for as yet she seemed not to have realized the nature of her ailment. It was perhaps fortunate that a toothache developed on December 20, permitting the diversion of dental consultation and roentgenographic study of the entire mouth. It was decided to extract two adjacent offending teeth. After stepping up the dose of penicillin these teeth were removed by Dr. Harold S. Vaughan on December 30. They were devitalized teeth and came away in fragments after considerable trauma to the bone. Profuse and continuous hemorrhage followed, and the hemoglobin fell from 81 per cent (13.5 Gm.) on December 27 to 72 per cent (12 Gm.) on January 3. The spleen could not be palpated on January 3, or thereafter.

The dose of penicillin was reduced to 3,000 units on January 7 and to 1,000 units on January 10, and the drug was discontinued on January 17. The small transfusions were continued to correct the anemia, and, on January 26, menstruation, which had been absent since April, re-

appeared. The patient was discharged on January 30, at which time she weighed 51.8 kg. She has continued to improve. On February 27, she reported her weight as 125 pounds (56.8 kg.), as compared with a normal weight of 130 pounds before her illness. On June 15, 1944, she

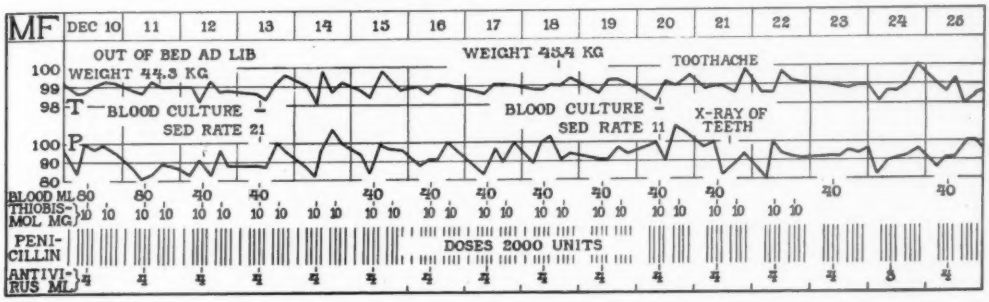

Fig. 15.

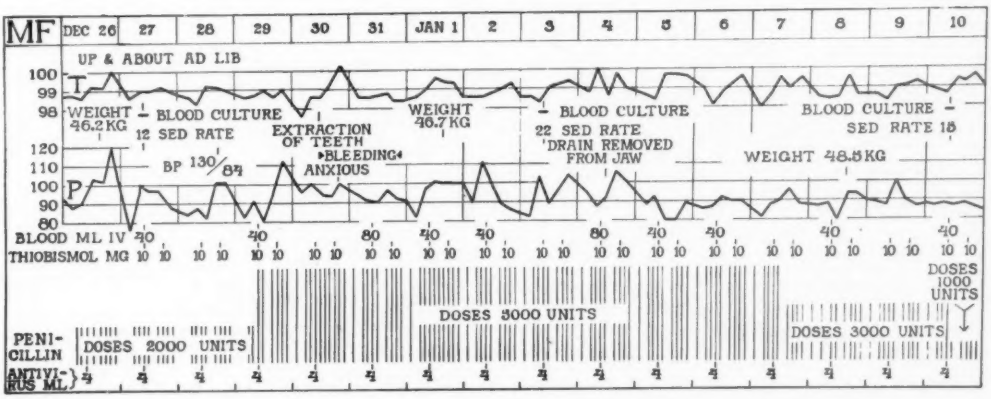

Fig. 16.

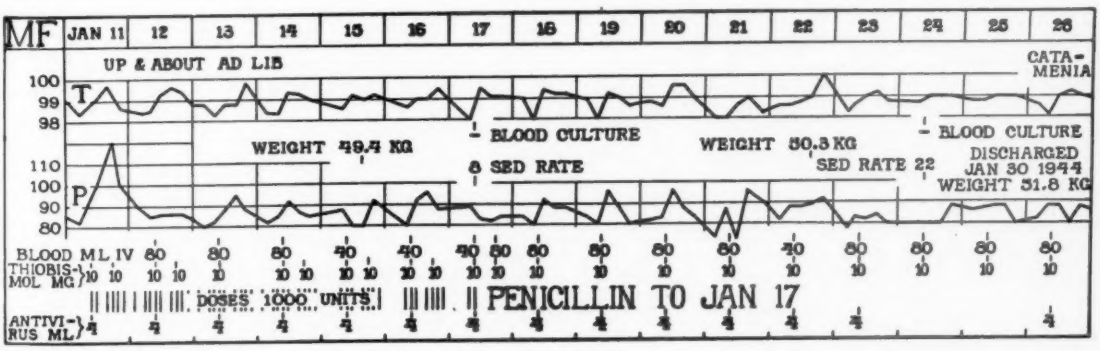

Fig. 17.

returned for examination. At this time she weighed 136 pounds (61.7 kg.), and had been restricting her diet to avoid becoming obese. The hemoglobin was 13 Gm. per 100 c.c. of blood; the erythrocyte count was 4,260,000, and the leucocyte count, 9,000. The blood pressure was 160/103. The patient ascribed the elevation of blood pressure to excite-

ment, and stated that her systolic pressure at home a few days before had been 128. The loud systolic mitral murmur was present as before. Her general appearance was excellent, and she was planning to go north with her family for a vacation of two months.

COMMENT

For the treatment of this patient there were expended approximately 4,864,000 units of penicillin, enough to terminate the active stage of inflammation in eighty cases of gonorrheal urethritis, an expenditure which may be deemed extravagant in the present emergency. We venture to suggest, however, that the morale of the men on foreign duty may be bolstered somewhat by the thought that the wife of a medical officer on duty overseas and the mother of his children has been given a chance to survive to greet him on his return. There has been some question concerning the use of the sulfadiazine, thiobismol, neoarsphenamine, antivirus filtrate, and citrated blood. These agents were not of themselves adequate to overcome the disease in this case. They were employed because they have seemed to exert a helpful influence in our previous experience with numerous patients, and especially because of the results of therapeutic tests in experimental endocarditis in animals.[6-10] Our purpose was not merely to demonstrate the value of penicillin, but rather to preserve the life of the patient, and to ensure, if possible, a long period of arrest in the activity of the infection. The record speaks for itself, and few will doubt the outstanding bacteriostatic effect of the penicillin, which was easily demonstrated in vitro as well as in vivo. We hope and believe that we have erred on the side of overtreatment, and, if the present state of arrest persists in this case, it will suggest that the therapeutic efforts were perhaps too elaborate.

Since improvement became evident in the case of M.F., there have come under our care fifteen more patients with endocarditis. Of these, there were nine in whom the infecting organism was *Str. salivarius*, or a closely related type of streptococcus. Two of these patients are dead; three are in the stage of clinical arrest and have been discharged from the hospital; four are still in the hospital under treatment or observation. The other six patients had endocarditis in different etiological categories. Of these, one is dead, two are in the arrested state and discharged, and three are still under care in the hospital. All the discharged patients have been returning at regular intervals for examination. We have not selected the cases, and no patient has been refused or excluded because of the advanced stage of the disease. In general, we consider the prognosis more favorable in young persons and in those who have been ill only a short time.

We deem it a privilege to make grateful acknowledgment to the Blood Bank of Queens County, Inc., and to the physicians of the Medical Society of the County of Queens who made available an adequate supply of blood for the wife of an absent fellow member. The penicillin was supplied from research allocations, under grave

difficulties, by Rare Chemicals, Inc., of Flemington, New Jersey, and by Charles Pfizer and Company, Inc., of Brooklyn, New York. It is a peculiar pleasure to salute Mr. John L. Smith, Vice-President of Charles Pfizer and Company, who, because of his broad humanitarian vision and keen scientific interest in the problem, deserves to be designated as the Abou ben Adhem of modern therapeutic research in bacterial endocarditis.

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Abstracts and Reviews.

Selected Abstracts

Shuler, R. H.: Kupperman, H. S., and Hamilton, W. F.: Comparison of Direct and Indirect Blood Pressure Measurements in Rats. Am. J. Physiol. **141**: 625, 1944.

Simultaneous readings of systolic pressure of rats from the Williams, Harrison, Grollman apparatus and from direct arterial puncture showed that pressures obtained by them were too low and that the disagreement was variable. Addition of 40 ± 10.7 mm. Hg to published figures will bring them to about the right value.

Substitution of a 16 mm. cuff for the 40 mm. cuff or 26 mm. cuff gave readings which were consistently 36.5 ± 5.6 mm. Hg low, and which were less variable. A 5 mm. cuff gave much truer readings. They were accurate at 120 mm. Hg, but somewhat too high above that level, and too low below that level. These errors can be corrected. The use of a ½ mm. capillary tube for the oncometer gave sharper end points, greater reproducibility and eliminated the need of heating the rats and of training the observer.

AUTHORS.

Patras, M. C., Brookhart, J. M., and Boyd, T. E.: Respiratory Effects on the Filling of the Ventricles During a Prolonged Diastole. Am. J. Physiol. **142**: 52, 1944.

Ventricular volume was recorded by means of a cardiometer in the closed chest, the recording system being so arranged that external pressure on the ventricles followed the normal respiratory variations of intrathoracic pressure. Diastole was prolonged by vagal stimulation.

Under these conditions, ventricular filling at any stage of diastole is accelerated by inspiration and retarded by expiration. If either inspiration or expiration occurs while filling is in progress, the gradient of the filling curve is altered thereby. The volume curves thus very considerably in form. Such variations are particularly prominent during the stage of diastasis.

The effects described become less conspicuous as the mean level of venous pressure is raised, but are still demonstrable when venous exceeds intrathoracic pressure by 90 mm. of water.

AUTHORS.

Holt, J. P., and Knoefel, P. K.: Changes in Plasma Volume and Cardiac Output Following the Intravenous Injection of Gelatin, Serum, and Physiological Saline Solution. J. Clin. Investigation **23**: 657, 1944.

Plasma volume, arterial and venous oxygen content, oxygen consumption, arterial blood pressure, right auricular pressure, and the hematocrit were determined in normal barbitalized dogs, before and after the intravenous injection of 50 c.c. per kg. body weight of 0.9 per cent sodium chloride solution, gelatin solution, and serum. Blood volume, cardiac output, total peripheral resistance, and the oxygen content of 100 c.c. of arterial red cells were calculated.

Sodium chloride solution gave a small and brief increase in plasma volume. Gelatin solution and serum gave a greater and more sustained increase in plasma volume.

The injection of these solutions caused the cardiac output to increase and the total peripheral resistance to decrease.

No consistent quantitative relationship was found between blood volume and cardiac output, between blood volume and right auricular pressure, or between cardiac output and right auricular pressure.

Blood serum and a 3.75 per cent gelatin solution are about equally retained in the vascular bed, both to a greater extent than is 0.9 per cent sodium chloride.

AUTHORS.

Donovan, G. E.: Phono-Electrocardioscopy. Lancet **1**: 500, 1944.

The author has designed an instrument for amplified auscultation, phonocardiography, electrocardiography, and sphygmography which he calls a phonoelectrocardioscope. The instrument permits: simultaneous, direct, continuous, visual recording of the phonocardiogram and electrocardiogram, plus amplified auscultation; simultaneous, direct, continuous, visual recording of the phonocardiogram and sphygmogram, plus amplified auscultation; simultaneous, direct, continuous, visual recording of a stethoscopic phonocardiogram and linear phonocardiogram of the same area plus amplified auscultation; simultaneous, direct, continuous, visual recording of the phonocardiogram of one area with that of another, plus amplified auscultation; simultaneous, direct, continuous, visual recording of any pair of the electrocardiographic leads, such as Leads I and III; observation for any length of time; detailed visual analysis. The reserve gain of the amplifiers and the wide range of time-base speeds make possible traces of any size considered desirable; photographic registration of the traces; accentuation of murmurs of desired sounds and attenuation of unwanted ones.

The instrument is described in detail and its advantages are pointed out. It should be useful in all forms of cardiology.

MCCULLOCH.

Clagett, A. H.: The Electrocardiographic Changes Following Artificial Hyperpyrexia, Am. J. M. Sc. **208**: 81, 1944.

While the majority of electrocardiographic changes following fever therapy are insignificant and probably due to the effect of tachycardia, it is possible to have changes due to severe myocardial damage, such as that caused by occlusion of a small coronary artery.

In those cases with myocardial damage due to fever, one should not give a good prognosis merely because the patient is young and the causative agent (fever) has been removed. The treatment of these cases should be the same as that given myocardial infarction due to any other cause.

AUTHOR.

Faulkner, J. M., and Duncan, C. N.: The Significance of Marked Left Axis Deviation of the Electrocardiogram. Am. J. M. Sc. **208**: 205, 1944.

An attempt was made to correlate marked left axis deviation of the electrocardiogram with significant clinical and post-mortem findings. A study of the clinical records in two hundred cases revealed that 51.5 per cent had no underlying reason for, or evidence of, left ventricular enlargement.

Measurements of the heart from teleoroentgenograms in ninety-seven cases were within normal limits in thirty-five cases (37 per cent). In twenty-seven autopsied cases the heart was entirely normal anatomically in the older age groups.

AUTHORS.

Wenner, H. A.: Notes on Congenital Auriculo-Ventricular Dissociation: Report of a Case of Congenital Complete Heart Block. Connecticut M. J. **8**: 160, 1944.

The clinical history of a 6-year-old girl with congenital heart block and Adams-Stokes attacks has been described. A résumé of the clinical and pathologic findings in congenital heart block has been presented.

AUTHOR.

Thomas, W. C., and Harrison, T. R.: The Effect of Artificial Restriction of Activity on the Recovery of Rats From Experimental Myocardial Injury. Am. J. M. Sc. **208**: 436, 1944.

Following experimental injury to the hearts of rats the mortality is decidedly greater when the animals are kept closely confined in small cages which restrict muscular activity.

Animals so confined display considerably less activity, as measured by the work adder method, than control animals allowed to wander freely about in larger cages.

Observations with the optional treadmill have shown that following injury to the heart the rat tends to return to the preoperative level of exercise within a period of three to seven days.

Enforced strenuous muscular effort even when carried out within twenty-four hours after cardiac injury, did not materially increase the mortality in rats. Likewise, such exercise carried out in three or more days after the operation did not cause a significant increase in mortality.

The question of the desirability of prolonged and rigid rest in bed following myocardial infarction in patients has been discussed and it has been pointed out that this procedure has serious disadvantages as well as some advantages. On the basis of the available evidence it would appear that during the first two weeks the advantages of strict bed rest probably outweigh the disadvantages, but that after this time the reverse is probably true.

AUTHORS.

Wainwright, C. W.: Dissecting Aneurysm Producing Coronary Occlusion by Dissection of the Coronary Artery. Bull. Johns Hopkins Hosp. **75**: 81, 1944.

A case of dissecting aneurysm is presented in which myocardial infarction was produced by dissection along the left coronary artery and its anterior descending branch. The lumen of the latter was occluded by the pressure of the hematoma within its wall. The clinical features of the case were those of both dissecting aneurysm and myocardial infarction. When typical signs and symptoms of both conditions are present, such a course of events as obtained here warrants clinical consideration and probably occurs with greater frequency than reports indicate.

AUTHOR.

Scott, G. E. M.: Rheumatic Infection in Childhood: A Survey From the Children's Hospital, Melbourne. M. J. Australia **2**: 309, 1943.

Six hundred forty-five cases of rheumatic infection occurring at the Children's Hospital, Melbourne, are examined, and the mortality rate is shown. In contrast to most statistics, there is a small preponderance of male patients. The age incidence has been found to be slightly higher than the average. The question of

symptomatology and of the occurrence of carditis is discussed, together with investigational methods. Reference is made to the problem of treatment, and its importance is stressed.

AUTHOR.

Cornell, A., and Shookhoff, H. B.: Actinomycosis of the Heart Simulating Rheumatic Fever. Arch. Int. Med. 74: 11, 1944.

Involvement of the heart in actinomycosis is rare. Analysis of three new cases and of sixty-five others collected from the literature shows that the heart may be involved by direct extension of the infection from a neighboring organ (most commonly the lungs) or by metastasis through the blood.

Metastatic involvement rarely produces clinical signs. About half of the patients in whom involvement of the heart is by direct extension show clinical manifestations.

The most common clinical manifestation in cardiac actinomycosis is congestive heart failure. A pericardial rub was heard in three cases and cardiac murmurs in only two.

AUTHORS.

Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program. J. A. M. A. 126: 84, 1944.

Acute rheumatic fever shows a striking geographic variation in its distribution, as indicated by the incidence rates per thousand troop population in the various geographc areas.

Acute rheumatic fever occurring in high incidence during this study in every instance has been preceded by a high incidence of hemolytic streptococcus infections.

A 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcic infections has been accomplished by the use of sulfadiazine prophylaxis under carefully controlled conditions and on a significantly large troop population. No serious drug reactions occurred.

From the partial data at hand, it appears that the reduction in rheumatic fever parallels that of respiratory and streptococcic diseases.

The possibility of utilizing these prophylactic methods, thus saving millions of hospital days, avoiding serious complications, and adding millions of effective man days to the war effort, should be given consideration.

AUTHOR.

Fox, T. T., and Bobb, A. L.: Cardiac Arrhythmias in 1,000 Cases of Pulmonary Tuberculosis. Am. J. M. Sc. 208: 201, 1944.

Pulmonary tuberculosis does not affect the incidence of abnormal cardiac rhythm or abnormalities in the conduction mechanism. In the majority of cases presenting these abnormalities, other clinical or laboratory evidence of intrinsic, cardiovascular involvement can be elicited.

It is suggested that right pulmonary lesions involving the mediastinum may constitute an extracardiac factor in the causation of arrhythmias and conduction abnormalities in a *previously* diseased myocardium.

AUTHORS.

Mosenthal, H. O.: Development of Hypertension Associated With Lesions of the Kidney. Am. J. M. Sc. 208: 210, 1944.

Unilateral renal disease may exist for many years without affecting the blood pressure. As compensatory processes for the maintenance of normal arterial tension became strained, periods of intermittent rise in blood pressure occur. Finally, a permanent hypertension may develop. The extirpation of a unilaterally diseased

kidney should prevent a rise in blood pressure, or remedy it if it has become permanently established, provdied there are no causes for hypertension either in the remaining kidney or elsewhere in the body.

AUTHOR.

Thomas, C. B.: Experimental Hypertension From Section of Moderator Nerves: Relationship of the Acute Pressor Response to the Development and Course of Chronic Hypertension. Bull. Johns Hopkins Hosp. **74**: 335, 1944.

The acute and chronic pressor responses are of similar magnitude and general character in a given animal.

A depressor influence usually appears within a few minutes of the maximal acute pressor response following moderator nerve section, which brings the pressure down to normal for a day or two and which may be present in some degree for several weeks.

Chronic hypertension usually appears within forty-eight hours after complete moderator nerve section, and disappears only if nerve regeneration occurs.

AUTHOR.

Morton, B. M., Shearburn, E. W., and Burger, R. E.: Synthetic Vitamin K and the Thrombosis of Veins Following Injury. Surgery **14**: 915, 1943.

A group of experiments performed to study the possible influence of vitamin K on thrombus formation in dogs has been described. The radial and saphenous veins of the legs of fifty-two dogs were traumatized mechanically by sacrifying the intima with a hooked needle. The veins were removed at forty-eight- and ninety-six-hour intervals afterwards. Twenty-seven of the animals received a surplus of synthetic vitamin K along with the regular diet for a week prior to the injury, and the remaining twenty-five were utilized as controls. Prothrombin times, hematocrit determinations, and clotting times were made in each animal at intervals, without any demonstrable effect of synthetic vitamin K administration.

The incidence of thrombosis after injury to the intima of the veins was not significantly increased coincident with the administration of synthetic vitamin K, being 33 per cent in the control group and 38 per cent in the vitamin K group. The small difference does not seem important. The prothrombin values, which are important in the coagulation process, did not significantly change after the administration of synthetic vitamin K. There was no significant difference in the results obtained by the Squibb and Abbott synthetic preparations. Those dogs with a hematocrit reading below 40 per cent, however, revealed a slightly higher incidence of thrombosis in both the control and vitamin K fed group.

Clinically, the incidence of thrombophlebitis has been less in the University of Virginia Hospital in the smaller group of women given vitamin K just before or at the time of delivery than in the larger group receiving no exogenous vitamin K except in the normal diet.

AUTHORS.

Davis, B. D.: The Indirect Measurement of Mean Venous Oxygen Tension During Anoxia. J. Clin. Investigation **23**: 666, 1944.

A method is presented for determining the mean venous oxygen tension ($MVpO_2$) indirectly by means of equilibrating gas mixture of low pO_2 with pulmonary arterial blood. Reproducible results were produced under standard but nonbasal conditions, ranging, in fifteen individuals, from 26 to 32 mm. Hg at atmospheric pressure.

Observations at simulated altitudes of 8,000 to 20,000 feet indicated that the cardiac output rose progressively with altitude, reaching 189 per cent of normal at 20,000 feet. This circulatory compensation decreased the tissue anoxia at the

various altitudes by 40 per cent, the $MVpO_2$ at 20,000 feet being 19.8 mm. rather than the value of 13.5 mm. which would have obtained if the cardiac output were constant.

AUTHOR.

Bollman, J. L., and Flock, E. V.: Changes in Phosphate of Muscle During Tourniquet Shock. Am. J. Physiol. **142**: 290, 1944.

The changes which occur in the phosphates of muscle, the blood supply of which has been completely occluded, are those of autolyzing muscle. Adenosine triphosphate almost disappears after three hours and phosphocreatine is almost completely hydrolyzed in one hour. The inorganic phosphates of the muscle rapidly increase to a maximum in about four hours. The total of the acid-soluble phosphates is not changed. If the flow of blood is restored to the muscle within three hours there is resynthesis of adenosine triphosphate and phosphocreatine with a corresponding decrease of the inorganic phosphate. Fatal shock does not develop even though large amounts of muscle have been occluded. When the occlusion is released after more than three hours there is no regeneration of adenosine triphosphate or phosphocreatine but considerable inorganic phosphate is washed from the injured muscle into the blood. Fatal shock develops in rats so treated if the muscles of more than one leg and thigh have been occluded for three and a half hours or if the occlusion of only one thigh and leg persisted for six hours before release. This type of shock is definitely not due to adenosine triphosphate washed out of the muscle because adenosine triphosphate is destroyed during the occlusion and its decomposition products appear to be relatively nontoxic. In rats surviving release after occlusion of one leg for four hours there is almost complete necrosis of the injured muscle but sufficient cells remain alive to restore themselves. After four to six weeks there is restoration of function of the leg, although the original size of the muscle bundles is not completely restored.

AUTHORS.

Sherman, C. F., and Ducey, E. F.: Cardiac Mensuration. Am. J. Roentgenol. **51**: 439, 1944.

A direct comparison was made between the transverse cardiac diameter of two hundred adult males, obtained within ninety days of death, and the weight of their hearts at autopsy.

In this study, the results by the Ungerleider method are much more closely correlated with the actual cardiac weight than are those of the other two roentgen methods studied.

There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight as calculated from Zeek's table. This correlation expressed numerically has a value of 1 to 3.3.

Marked deviation from normal body weight and pericardial effusion greater than 200 c.c. impair the accuracy of the method to such an extent as to preclude its use without qualification.

AUTHORS.

Mazer, M., and Wilcox, B. B.: A Simple Graphic Method for Measuring the Area of the Orthodiagram. Am. J. Roentegnol. **51**: 444, 1944.

A simple graphic method for the determination of the area of the orthodiagram is described. It requires no equipment not readily available to any physician. Its application to one hundred cases checked by the planimeter shows it to have a sufficiently high degree of accuracy for clinical purposes.

AUTHORS.

Gage, I. M.: The Technical Simplicity of the Matas Endo-Aneurysmorrhaphy. Ann. Surg. **119:** 468, 1944.

Endo-aneurysmorrhaphy is the surgical procedure of choice in treating aneurysms of the peripheral arteries. There are only two types of endo-aneurysmorrhaphy that are applicable to aneurysms of the peripheral arteries: The restorative (saccular) type; and the obliterative (fusiform) type. An adequate and sustained collateral circulation must be present and satisfactorily demonstrated before the operation is undertaken. The collateral circulation can be developed by two methods: Mechanical (Matas method), and physiologic (blocking out the sympathetics, the author's method). Absolute hemostasis must be obtained and continued until the intrasaccular toilet is completed. This operation is contraindicated in all arterial aneurysms in which the blood supply cannot be unequivocally controlled during the entire operation. It is the simplest of all surgical procedures used for the cure of arterial aneurysms.

AUTHOR.

Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin. Am. J. M. Sc. **208:** 54, 1944.

A simple, safe, and practical method for the subcutaneous administration of heparin has been devised. Its clinical application has been successfully attempted in fifteen cases of thrombophlebitis and phlebothrombosis.

With the technique of subcutaneous administration of heparin as here described, no instantaneous withdrawal of the heparin effect is as yet feasible. However, whole blood or protamine may be employed to neutralize the free heparin, while compression about the site of inoculation will effectively suspend its further liberation. This was demonstrated in a case of subacute bacterial endocarditis successfully heparinized by this method. Injections were made, as usual, in the lateral or anterior aspect of the thigh. Compression was effected for one to three hours by means of a tourniquet above or a compression cup about the site of injection. The use of this subcutaneous method of heparinization, while not yet commercially available, gives promise of sharply curtailing the cost of this anticoagulant agent because of the reduced heparin requirement and ease of administration.

AUTHORS.

Smull, K., Wégria, R., and Leland, J.: The Effect of Sodium Bicarbonate on the Serum Salicylate Level. J. A. M. A. **125:** 1173, 1944.

When a serum salicylate level has been established and is being maintained by the oral administration of enteric coated tablets of sodium salicylate, the simultaneous administration of approximately equal amounts of sodium bicarbonate results in a definite fall of the serum salicylate level.

The simultaneous administration of equal amounts of sodium bicarbonate and enteric coated sodium salicylate prevents the establishment of as high a serum salicylate level as would be obtained with sodium salicylate alone.

AUTHORS.

Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients With Cardiovascular Disease. J. A. M. A. **125:** 1075, 1944.

A review of some recent experimental evidence and certain clinical considerations leads to the following general conclusions:

Extreme restriction of body movement causes increased mortality in animals with experimental myocardial injury.

There is no proof that rest in bed carried out for many weeks after symptoms have disappeared is of value in the physical management of the patient with con-

gestive failure, angina pectoris, or myocardial infarction. The available evidence, while perhaps not conclusive, points to the contrary and more especially so if the recumbent posture is enforced while the patient is kept in bed.

From the psychic standpoint there is a definite disadvantage in the enforcement of a rigid regimen after the acute phase of the illness has subsided.

Until more definite information is available, the following tentative suggestions are offered for a plan of treatment which obviously requires modification according to the status of the individual patient:

a. Persons with congestive heart failure should be allowed out of bed for several hours a day, as soon as severe dyspnea at rest has subsided.

b. Following myocardial infarction, recumbency should not be prescribed for a longer period than two to three weeks after the more acute and alarming symptoms have subsided. The recumbent position should not be enforced on patients who are more comfortable sitting. Other things being equal, it would appear wise to allow elderly patients out of bed sooner than younger ones.

c. Rest in bed for more than a day or two at a time probably has no place in the treatment of angina pectoris except in those patients who are especially liable to develop myocardial infarction in the immediate future, as indicated by increasingly frequent and prolonged attacks at rest.

d. In all patients with the severe forms of heart disease, activity should be kept below the symptomatic threshold, i.e., should be less than that amount which induces dyspnea or pain.

AUTHOR.

Levine, S. A.: Some Harmful Effects of Recumbency in the Treatment of Heart Disease. J. A. M. A. **126:** 80, 1944.

Rest in bed, which has been the backbone of our treatment of heart failure, needs reconsideration in the light of some possible harmful effects.

There is both clinical and laboratory evidence to show that recumbency may be very harmful for certain patients with heart failure. The heart may be made to work more rather than less, and pulmonary congestion may be made worse rather than better at certain stages of heart failure by placing the patient in bed. Making the bed slant downward by placing 9-inch blocks of wood under the headposts is a simple method of minimizing this undesirable effect. At times it is wise to treat patients with heart disease in a chair rather than in bed.

Cardiac as well as noncardiac patients who are confined to bed for any appreciable length of time should be instructed to exercise their legs frequently or to have massage of the legs to prevent venous thrombosis of the legs and pulmonary emboli.

AUTHOR.

Erratum

In the September, 1944, issue of the JOURNAL, Vol. 28, p. 298, the article by R. M. Tandowsky, Norma Anderson, and J. K. Vandeventer, entitled "An Electrocardiographic and Clinical Study of Various So-Called Cardiac Drugs," should be corrected as follows: In Table I, page 299, the sixth line in the second column should read: 3 c.c., 1.5 cat units; the last line in the first column should read: Metrazol (Bilhuber-Knoll). On page 303, Digalin, on Fig. 7 should be Digalen. On page 306, Fig. 11, Metrazol should be followed by (Bilhuber-Knoll). On page 307, Fig. 13, Digalen should appear above the second tracing, and Scillaren above the third tracing.

American Heart Association, Inc.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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